NOV 11 1929

VOL. CLXXVIII, No. 5 NOVEMBER, 1929 No. 692

THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1929

ORIGINAL ARTICLES.

ARTHRITIS.*

By Ralph Pemberton, M.D.,

CHAIRMAN OF THE AMERICAN COMMITTEE FOR THE CONTROL OF RHEUMATISM, VISITING PHYSICIAN, PRESBYTERIAN HOSPITAL, PHILADELPHIA.

The opportunity of speaking upon the subject of arthritis is welcomed because the invitation to do so carries with it evidence of the awakening appreciation on the part of the profession for the great problem involved. Arthritis and rheumatoid disabilities constitute the oldest disease entity of which there is any record, as is amply illustrated in the fossilized remains of the reptiles of the cretaceous period, long antedating the advent of man. Men of the Old Stone Age suffered from arthritis, and it was, as one writer put it, the disease par excellence of the Egyptians. It was a cause of so much disability to the Greeks and Romans as to account for the establishment of such natural spas as Aix Les Bains in France, which has had a continuous existence of two thousand years. Notwithstanding this, and the importance of the disease as one of the great problems of medicine, arthritis has received less intensive and concerted attention than have many disturbances of lesser import.

Owing partly to the refractory nature of the disease itself and partly, perhaps, to a sort of obloquy reflected from certain irregular cults of treatment, a curious inertia seems to have characterized the attitude of the profession as a whole toward arthritis for many decades. Interest and investigation in this great field have definitely not kept pace with the advance of medicine as a whole.

* Mary Scott Newbold Lecture (delivered at the College of Physicians, Philadelphia, November 7, 1928).

Horace says in one of his odes "Rusticus expectat dum defluit amnis" ("the rustic waits for the stream to run by"); and one might conclude that the profession has alike waited for the constant stream of arthritics to dry up.

Fortunately, a sharp awakening from this attitude of indifference has recently come about. A chief factor in this has been the establishment nearly everywhere of provisions for insuring the working classes. As has not infrequently happened in medicine, interest in the problem was brought about partly through the back door, so to speak, and the profession, especially in Europe, is now somewhat in the position of being goaded on by the demands of the "sick funds" organizations, that something be done to reduce their losses from arthritic and rheumatoid disability. It will come as a surprise to some to learn that in Berlin alone, the incidence of rheumatoid disability is 3.4 times greater than that due to tuberculosis. In England, one-sixth of the sum expended under National Insurance Acts was for diseases classed as rheumatic, and half of this was for chronic arthritis alone. In Sweden, four hospitals have been created for the exclusive care of chronic arthritics. In London, a very large clinic is being established under the auspices of the Red Cross for the purpose of extending the benefits of physiotherapy in a wide sense to sufferers from arthritis. Many other instances of the kind could be cited which show beyond doubt that for the first time in the history of medicine something approaching a concerted attack is being made upon this disease.

It is of much significance to note that within the last two years a committee for the study of arthritis has been established in this country, largely under the originating impetus of Dr. Louis B. Wilson, director of the Mayo Foundation, whose attention was called abroad to the importance of the problem. This committee consists of a dozen representative men chosen from geographical extremes of the United States and Canada and has held two meetings. Reference will be made to some of the steps planned and taken.

In general, the attitude of the profession in Europe toward arthritis has been marked by somewhat more catholicity, especially as regards etiology than has been the case here during the past ten years and the American committee has reached a somewhat comparable viewpoint. One of the first steps undertaken by it was an attempt at simplification of classification, long the bugbear of students of the subject. It has been decided to recognize two great types of arthritis, atrophic and hypertrophic. This is in fact, under other names, the classification into the proliferative and degenerative types of Nichols and Richardson. All types of arthritis, exclusive of tuberculous, are included under these heads. The outstanding pathologic deviations are, in the atrophic type, smothering and destruction of cartilage by overgrowth of the synovial mem-

brane, together with a destructive growth of granulation tissue from the bone below; and, in the hypertrophic type, fibrillary degeneration of cartilage together with overgrowth of bone at the margins of the joint and elsewhere. Manifestations of the same underlying processes occur in the soft tissues also, but fall, more particularly perhaps, under the head of the atrophic variety. It is important to note, as Charcot pointed out in his Salpêtrière lectures forty years ago, that arthritis and rheumatoid disability are only branches of a large pathologic tree which has its roots in disturbances of widespread underlying physiologic processes.

In a brief article such as this, however, there is no opportunity to present at length the many factors in etiology, pathology, or treatment which must be considered in any thorough review of the subject. It is rather the purpose of this paper to sound some of the newer significant notes in relation to the disease. In this connection an important conclusion of the American committee on arthritis must here be mentioned, which may come as something of a surprise to many who have accepted whole-heartedly the rather crystallized opinion in this country of the cause of arthritis. Recognition of the importance of focal infection in a host of diseases has marked a signal advance in modern therapy and reflects credit upon American medicine more than upon that of any other country. In no other disease has the importance of focal infection been more apparent than in the case of chronic arthritis, particularly in relation to the many varieties of streptococci. So much has this been the case, that, in many quarters, the rheumatoid problem has been regarded as one solely of bacteriologic nature. Suffice it to state then, that, in the views of many of the committee, focal infection or infection of any kind, though in no sense to be minimized, constitutes often only an episode in the causation of the disease, acting like "the match to the priming." Indeed, the committee has placed itself on record as believing that the underlying causes are often farther to seek and are to be found, in part at least, in that background determined by heredity, constitutional make-up, the equilibrium of the nervous system, chemical and other toxins of imponderable nature and, finally, the conditions of the environment. This may seem somewhat too inclusive a statement and yet it is only with full consideration of the lines here implied, in the opinion of many of the committee, that successful treatment of the disease can be carried out. One natural result of the brilliant development which bacteriology has undergone in the past five decades has been a somewhat mechanical view of the depredations of bacteria in their effects upon tissues. Wells points out, however, that practically all bacteriologic processes are at last analysis chemical in nature.

Thus, it is the view of Zinsser that rheumatic fever is an allergic condition in which the body is sensitized to a bacterial antigen. He believes this to be the only explanation consistent with the

varieties of bacteria isolated through the interesting work of Small, Swift, Clausen, and others and with the frequency with which such factors as exposure seem to precipitate the attack. Swift remarks that it is easy to understand that the state of the tissues of the patient is the most characteristic feature of the disease and that the specificity of the streptococci recovered, may play a relatively unimportant rôle. Recent evidence suggesting the passage of certain strains of streptococci from one to another is in line with this view.

It seems highly probable, by analogy, that the atrophic forms of chronic arthritis may often have a comparable cause. As long ago as 1920 the present writer[1] advanced the then somewhat iconoclastic view, based upon observations in the army, that acute inflammatory rheumatism and the exacerbations of chronic arthritis seem to differ in degree rather than in kind.

The toxicity of extracts of the organisms isolated by Small and by Birkhaug, to mention only one influence, is so marked as to lead to the hope that among arthritics as a whole, a group may be found which will stand in some specific relationship to these or comparable organisms.

In view of these several considerations, it would appear that even the bacteriologic causation of arthritis proceeds in many cases from a wider premise than has been generally appreciated. Zinsser[2] says, "It is our opinion that in that branch of general physiology which is spoken of as immunology, we have been hampered in our reasoning by adhering too closely to analogies furnished by a few antigenic substances such as bacteria, animal cells and coagulable proteins. We are actually dealing with phenomena of much broader physiological interest." It is pertinent, therefore, to quote one sentence from a little brochure or primer which has been prepared by the American Committee for the Control of Rheumatism for distribution to the laity and, indeed, somewhat to the profession also.

"The commonest causes of atrophic arthritis are the poisons which are set free in our bodies. These poisons may be manufactured by the growth of germs which the body's defense mechanisms are too weak to resist or by a disturbance of normal physiology and chemistry of the body which may result from overtire and the bad use of our bodies."

In this connection should be mentioned another of the acknowledgedly prime factors in the causation of arthritis, especially of the hypertrophic type, in women—the menopause. The relationship is so clear that some students, have described specifically "arthritis of the menopause." In the view of some observers including Knaggs, Cecil, Osgood and Goldthwaite, hypertrophic arthritis is not of infectious or bacteriologic origin. Space has been given to the several considerations so far mentioned, because it is believed that they con-

stitute a new "take-off" in the approach to arthritis, of significance, in treatment, to the many sufferers from this disease.

The present is not the time for consideration of statistics except to mention that arthritis as a whole affects women with about twice the frequency of men, that the knee is the site of greatest involvement in all groups, the fingers coming next, and that in a study based upon 1100 cases by Dr. Peirce and the writer,[3] heredity played a rôle of unsuspected importance, being obvious in 60 per cent.

Study of the morphologic changes in the arthritic syndrome has been exhaustive but study of the dynamic pathology causative of the changes has been in general meager. How are they brought about? It is impossible to investigate a disease in which rarefication and overgrowth of bone are so conspicuous without being early impressed with the fact that it is necessary to invoke chemical reactions, in part at least, to explain the changes involving the calcium and magnesium of osseous tissue. Chemical analysis, however, of the fasting circulating blood along modern lines has been singularly unfruitful, although it has served to delimit the problem and direct attention into other channels. It may be said, however, that in arthritis as a whole, basal metabolism tends to be low; according to Swaim and Spear, chiefly in the degenerative type. It may be mentioned also that there is no apparent disturbance of the nitrogenous metabolism *per se*, and that there is no justification for withholding red meat from the arthritic as so long, and still so widely and erroneously, advocated. The frequency of anemia in arthritis and the importance of organs and other tissue for blood regeneration make this a matter of large importance.

It is only when one turns to a study of the arthritic by imposing on him a physiologic load of some sort, that one detects inadequacy of response, indicative of pathologic deviation.

One line of evidence, adduced in this way, came as the result of observing that certain low dietaries were of benefit to certain types of arthritis. In the attempt to throw light upon this through laboratory studies, it was ascertained that in the arthritic certain substances are removed from the blood, after ingestion by mouth, more slowly than is the case in health. In brief, 76 per cent of arthritics show actually or potentially a delay in the removal of dextrose from the blood and in this same blood there is also a higher percentage saturation of oxygen than normally occurs. Attempts to explain this phenomenon upon chemical grounds were unsuccessful and recourse was had to the hypothesis that the process was mechanical in nature, depending upon changes in the blood flow. Experiments were accordingly devised in which the circulation was cut off in three limbs, with the result that, upon feeding dextrose, it was possible to induce precisely the same phenomenon as occurs in the majority of arthritics. It thus appeared that the explanation

of the dextrose and oxygen values was referable to the failure of the blood to reach at least some tissues in which the removal of these substances normally quickly occurs. The cause of this interference with the circulation was conceivably to be found along the line of vasoconstriction. Attempts were accordingly made to ascertain whether the peripheral blood gave any evidence of this in terms of the blood count or other changes in the corpuscular elements.

In a series of careful studies, Dr. E. G. Peirce has shown that there tends to be a difference in the blood first issuing from peripheral capillary beds in the arthritic as compared with normal persons. This difference consists in a lower red-cell count in the first issuing drop as compared with later drops. In the normal, an opposite state of affairs obtains and the count of the first drop is higher than that of subsequent drops. This can be interpreted to mean that there are fewer cells in the peripheral vascular spaces of arthritics or that these spaces contain unduly large amounts of fluid. That these observations are not the result of chance or technical error is well illustrated by the fact that this low cell count in arthritis can be restored to normal by many of the measures which are of value clinically to the arthritic. Thus, exercise, the salicylates, coffee, external heat and massage induce a marked return toward the normal picture.

It then became desirable to check this further, if possible, by determining the actual state of the capillaries themselves and this was made possible by the method of direct inspection devised by Lombard fifty years ago and left buried until recently in the literature. A long series of studies was conducted upon normals and arthritics by Dr. Peirce, Dr. F. A. Cajori and the writer[3] as the result of which it has become reasonably clear that there is in arthritis a condition of the capillaries characterized essentially by a slow and interrupted bloodflow; constricted or, at all events, many empty vessels; and especially a generally "anemic" condition of the peripheral tissues studied. It has been possible fortunately to check this further by means of measures and drugs which benefit the arthritic and it was again found that following such measures as massage, exercise and aspirin the whole picture changes to one of adequate bloodflow, only to relapse again, however, upon cessation of therapy.

Dispassionate consideration of these several observations afforded striking evidence that at least part of the pathologic deviation productive of the symptoms and morphologic changes of arthritis is to be found in the altered state of the bloodflow in the finer vessels, probably in the nature of vasoconstriction. This is precisely in keeping with the clinical observation of the frequency with which Raynaud's syndrome is encountered in the rheumatoid state. It also fits in well with the long recognized clinical effect upon blood-

flow of the measures probably most used in arthritis, such as heat, massage, etc. It remained, however, for further experiment to place the matter upon a more secure footing. This experiment consisted in the attempt to interfere in the living animal with the circulation in the neighborhood of a joint. For this purpose, the writer's associate, Dr. A. D. Goldhaft, conducted a series of experiments in which the circulation to the patella was cut off by means of a purse-string suture carried around it. Six dogs were operated upon, using the other legs as controls. It was of the greatest interest to observe after some weeks, under the Roentgen rays, evidence of overgrowth of bone such as is seen in the patella of human beings suffering from hypertrophic arthritis of the knee. This result was forthcoming in every animal operated upon. That it was not due to the mechanical irritation of the operation, or of the silk ligature used, was shown by the fact that an equal amount of ligature placed near the patella without interfering with the blood supply, produced no change of organic or even functional nature. This experiment, then, coming as it did at the end of a series of observations all pointing the same way, is in agreement with the work of Wollenberg, and strongly suggests that the functional and organic changes of at least some kinds of arthritis, namely, the hypertrophic, are referable, in part at least, to a disturbance of the circulation. There is no opportunity here to point out the consequences which could be expected to follow anoxemia, not to say a relative anemia, of this kind but disturbance of the acid-base equilibrium is generally recognized to be one of them and the way is opened up for explanation of some of the changes, such as rarefication and overgrowth of bone, in which the fixed bases of the bone must necessarily take part. The tendency towards a lowered basal metabolism in arthritis is probably to be explained on the same basis, *viz.*, a curtailment of the finer bloodflow in at least the muscular tissues.

Another line of observation which must be briefly mentioned as of significance in the attempt to understand the mechanism of arthritis is to be found in the observation by Cajori and the writer that certain substances which reach the gastrointestinal tract through the mouth are carried directly, after absorption by the blood stream, to the joints themselves and can be redetected there almost immediately in the synovial fluid. Indeed, certain substances, presumably crystalloids, such as glucose, reach a higher concentration in the synovial fluid than may occur in the blood, possibly because the arterial blood supply to the joint exceeds the venous outgo. This observation affords definite evidence of a means of nourishment of the central avascular area of articular cartilage, a matter long in doubt. It also unmistakably proves that a variety of substances from the intestinal tract has access to the joint cavities. The possibility that deleterious as well as nutritive substances

from the bowel may here play a rôle must henceforth be definitely considered. It may be noted in passing that Freiberg has recently shown that sterile bacterial filtrates injected into the joint cavity of animals may produce changes characteristic of atrophic arthritis.

Treatment. It is axiomatic that study of the problem of arthritis has for its aim amelioration and prevention of the disease. A consideration of the rheumatoid problem from the viewpoint of such physiologic changes as are above described offers explanation of the rationale of many measures of value and suggests in an important way certain lines which treatment must follow. We do not know all that should and must be known about the disease but there can be no doubt that information at our command today enables us definitely to take a more hopefully constructive attitude than at any time in the past. As with many other diseases, treatment must take the direction of removing possible causes, removing or modifying the functional and organic changes which the disease produces, and finally, when necessary, adjusting the burden which a handicapped organism is asked to bear.

In the first connection, the question of focal infection comes prominently into the foreground but I take it that with the present audience there is small need to stress the recognized rôle which infectious processes may play. This rôle must have full emphasis in any consideration of treatment. That infectious processes do not constitute the whole picture, however, has already been stressed and is further evidenced by the fact that in 400 cases of arthritis among soldiers during the war, three times as many recovered in the presence of causative focal infection as got well following its removal. The sound position to take, of course, is to spare the subject all burdens of this nature compatible with good medical and surgical judgment after thorough and dispassionate analysis of the case. The duty of the practitioner, however, has only begun in most cases when abscessed teeth are removed or a boggy prostate is massaged.

There remains in chronic arthritis, following the removal of even causative infections, a more or less chronic dislocation of physiology which may persist a long time or even permanently. So much is this the case that one may almost say, once an arthritic, always potentially an arthritic. It was remarked earlier that constitutional and environmental circumstances play an important rôle in determining arthritis and there is today small doubt that the nervous system is importantly caught up in the production of the disease. This is amply illustrated in the most extravagant expressions which arthritis takes, namely, the grotesque bony overgrowths of Charcot's joint. Specific evidence to the same end is also seen in the experiments of Adson and Rowntree, who were able to relieve, at least temporarily in 2 cases, all symptoms of severe atrophic arthritis of the legs by

the operation of lumbar sympathectomy. The frequency with which arthritis implants itself upon individuals of asthenic and enteroptotic build, forces upon the critical student of the subject the necessity of correcting the background if permanent results are to be achieved. In this connection one of the most useful lessons ever adduced has come from the Boston orthopedists who have developed a viewpoint of much wider value than the term orthopedic implies. This has to do with the rehabilitation of the deranged physiology in the chronic arthritic or the structurally inferior subject. The lesson is one which every internist should be able to apply to the neurasthenics and, indeed, many cardiac and other types of patients under his care. Speaking as an internist, the writer believes that internal medicine has, perhaps, regarded illness too often from the standpoint of the organs concerned and too little from the standpoint of the structure in which they are housed. As regards arthritis, the writer is strongly of the opinion that no one is qualified to approach this great problem who is not familiar with these measures of structural rehabilitation of the chronic invalid at large. In fully one-third of all arthritics this constitutes a foundation without which no substantial superstructure can be expected to rise.

In view of what has been said regarding the necessity of obtaining or maintaining a physiologic balance, it does not surprise us to learn that one of the most important measures to be instituted early in the treatment of the disease is rest. By this is meant systemic rest of the body as a whole and not necessarily rest of the affected part which is determined by other and local considerations. As regards the joints themselves, it is the belief of some of the most qualified observers that, in general, rest of the joint in atrophic arthritis is not desirable, whereas in hypertrophic arthritis rest of the joint affords removal of one of the causative etiologic factors. Many cases of arthritis originate in fatigue. Many more suffer fatigue from fighting the disease and from carrying on with the fox at their vitals. Fatigue is also an expression of toxicity and unless the sufferer be given a chance to recover from the lesser disability he will be quite unable to fight the greater.

Apart from the significance of rest as a specific measure, it has another importance in relation to various other forms of treatment, especially physiotherapy. Rest must be used in extra dosage, so to speak, when demands are being made upon the organism to respond to various therapeutic procedures, nearly all of which exact their toll of fatigue.

Perhaps the oldest, and certainly one of the most important categories into which treatment of the arthritic must fall is that of physiotherapy. Under the two great heads of massage and heat, sufferers from arthritis have in an untutored way themselves sought

relief through these measures over periods of centuries. The value of massage, exercise and heat to internal medicine at large is just beginning to be appreciated by the profession as a whole. The recent creation of the Council on Physical Therapy of the American Medical Association can be instanced in evidence of this, and it is said to have been one of the regrets of Dr. Weir Mitchell, whose name is so closely associated with this hall in which we are meeting, that his efforts at extending the use of physiotherapy fell so far short of the aims he had in view.

Orthopedic surgeons and neurologists, almost alone among medical men, appreciate fully the value of massage and heat. The proper prescription of these agents is almost a specialty in itself and it can only be added here that these measures serve the several purposes of relieving much suffering, restoring deranged physiology and modifying organic disturbances of structure.

Mention must be made of vaccine therapy and the use of nonspecific protein. The use of these measures springs directly from the bacterial origin of many cases of arthritis and needs no defense or emphasis in the treatment of infections. Their place in arthritis is established in relation to one exciting factor of the disease, but those who best understand the principles of operation best understand also the limits within which they should be employed.

The most hopeful sign in this connection proceeds from the allergic conception of the etiology of many cases of the atrophic type and it is to be hoped that the organisms isolated by Small, together with that of Birkhaug and, more recently, Cecil, may prove to be utilizable in the direction of desensitization or increased immunity.

Nonspecific protein therapy has its origin in somewhat comparable premises and is so widely accepted, even in the treatment of paresis by malaria, as to need no particular mention. Its value in arthritis, in a limited but definite number of cases, may depend in part upon certain antigenic or other specific properties, but it is also certain that part of the benefit is referable to the heightened metabolism induced. Instances are legion in which the symptoms of arthritis have disappeared entirely in the presence of hyperpyrexia from pneumonia or typhoid, with the increased metabolism and accelerated blood-flow which they inevitably bring about.

Vaccines and nonspecific protein should be used with a balanced appreciation of the nature of the disturbance and what they may be expected to accomplish. The limits and dangers of physiotherapy constitute part of the lesson to be learned in relation to that field; and by the same token, the limits and dangers of vaccine therapy are also to be kept in the foreground.

Co-equal in importance with the bacteriologic factors in arthritis, in the usual sense of the word, and possibly surpassing them, both

etiologically and therapeutically, is the great field constituted by the gastrointestinal tract. Apart from the question of local foci, such as an infected gall bladder or ulcerative colitis, the intestinal tract plays unquestionably a large rôle dependent upon the still unmapped processes of fragmentation of the foodstuffs and the formation of the products of normal bacteriologic activity. Ten years ago this conception had little acceptance; today, it is so widely appreciated that the laity are flocking with their well-known vogue for "cures" to the many establishments given over to colonic irrigation, facetiously referred to sometimes as "colon filling stations." As is usually the case with new ideas in medicine, enthusiasm for this procedure runs ahead of the facts and yet there can be no question that through this type of agency we have a means of removing or modifying one of the great causative factors of arthritis. The rationale of this measure is too complicated for detailed mention here but probably depends in part upon removal of the products of bacteriologic growth. That this is not the whole explanation, however, is pretty clear from the fact that change of the intestinal flora does not necessarily have any beneficial influence. Faulty anatomy and faulty physiology of the viscera and especially of the intestinal tract apparently afford the basis upon which the exciting factors can become operative.

If there be value in expediting out of the gastrointestinal canal its complicated and varied contents, it should and does follow that control of the intake of the substances thus sought to be expedited, should also be important. It is precisely that taken in by mouth which, in large part, is removed by irrigation. Beyond question, a large field of therapy here presents, the high points of which only can be outlined. The form which it takes is chiefly in the direction of a lowered caloric intake at large, though there is reason to believe that the starches and sweets are more deleterious than the other foodstuffs. The operation of a low dietary is probably dependent partly upon removal of the substrate on which the intestinal flora subsist but also upon an indirect metabolic influence, which cannot be developed here because of limitations of time. One of the basal facts relating to arthritis is caught up in the influence of a heightened bloodflow and increased metabolism upon the disease. By the same token, it is precisely when catabolism runs ahead of anabolism that the arthritic may experience temporarily some of the sharpest benefit. When a restricted dietary brings about this state of affairs, certain cell units are apparently not only spared a previous burden but they function with a reserve potential which, while the situation lasts, constitutes physiologic equilibrium. The dangers of undernutrition, however, present limiting factors in this type of therapy and it can be practised only with a balanced appreciation of both sides of the equation. When it happens, in suitable

sthenic cases, that a reduced dietary can be accompanied by the use of physiotherapy, not only is the physiologic load lightened but at the same time a metabolic fillip is also given to the flagging horse. The late Cardinal Gibbons is said to have remarked that he owed his good health to his bad digestion. Perhaps to few other types of invalids has this epigram such application in principle as to the chronic arthritic. If there were more dyspeptics, so to speak, there might be fewer arthritics.

The field of drug therapy, in general, has limited value in the arthritic syndrome. Heading the list as regards relief of pain are the salicylates in their various forms but, by and large, they serve only to afford temporary comfort and may have undesirable consequences. In the very early stages of muscular disability their use is not infrequently sufficient to restore a perverted physiology to normal and, upon restoration of function, the physiologic balance of health may be maintained.

Superseding the salicylates in value is arsenic, one of the dozen or more irreplaceable drugs of medicine. Its influence upon metabolism and regeneration of the blood elements is perhaps never more graphic than in some cases of arthritis which may for a time improve so rapidly as to lead to belief that the cure is at hand. Other measures, of limited value, can be grouped under the general caption of those which probably hasten metabolism, such as potassium iodid and the Roentgen ray. Orthoiodoxybenzoic acid, which has recently had a "flair," is a sort of glorified salicylate and has in general not justified the claims made for it by some writers.

Finally, mention must be made in this cavalier review of arthritis, of the importance of coördinating various lines of treatment. It is a fundamental principle in the treatment of disease that the given load must be adjusted to handicapped organs or systems. It is further axiomatic that the restorative powers of Nature alone achieve the processes of convalescence of repair. These facts are too often overlooked, however, in the care of the arthritic, and expectation is often entertained that a drug or injection will restore atrophied muscles or remove the fibrositis and faulty physiology productive of it.

Treatment of the arthritic, with the inevitably long period of convalescence, should be somewhat analogous to the training of an athlete. Professional trainers are unanimous as to the importance of a carefully-balanced programme for their charges. The athlete never runs when he is tired and he rests after his run. Massage further contributes to the efficiency of his normal muscular physiology. How much better the trainer of athletes understands the problems of his protegés than does the average physician the problem of the arthritic. The chronic arthritic is nearly always fatigued but is nevertheless usually asked to undergo at once a variety of

procedures, surgical as well as medical, which often reduce him to an even lower ebb. The writer cannot hope in the brief space here allotted, to discuss the details of the treatment of arthritis in the fullness they deserve. If, however, only one message could be given to this audience it should be an exhortation to maintain a wide-angled viewpoint in considering the rheumatoid problem; to coördinate the various sound measures of therapy critically and more frequently than is usually the case; and to appreciate that at last analysis it is not necessarily the removal of a focus or usually any single agent but rather a restoration of physiology along the many lines indicated which ushers the chronic sufferer from arthritis into channels of recovery. Pessimism has long dominated the attitude of the profession toward the chronic arthritic. A keynote sounded in the brochure of the committee already mentioned, is in the opposite direction, convinced, as many of its members are, of the great value of treatment in this disease. It is of the highest importance that more investigation be carried out on the causes and nature of arthritis. It is of equal importance, however, that there be wider dissemination of what is already known regarding the disease. With the measures now at our command thousands of arthritics throughout the country, probably doomed to wheel-chair invalidism, could be saved from this and often restored to active life if these measures could be intelligently and skillfully applied. Not only are there few other diseases in which intelligent, well coördinated treatment is so urgently required; there are in fact few other chronic diseases for which more can be done.

Arthritis touches more fields of medicine than does any other pathologic state. Its subtleties cannot be learned quickly or easily and it is a favorable augury that this problem is now in process of taking its place with tuberculosis and syphilis as one of the great chapters of medical science. Only when this has been achieved, however, will there arise that wealth of professional equipment which alone is adequate to combat it. We are today in this country in the struggle against arthritis more or less in the position of Trudeau fifty years ago in the fight against tuberculosis. Those of us who have been most interested in this problem are best aware of the inadequacy of individual effort and can only hope that the great mass of right-thinking laymen and medical men will rise, as they have so often done in the past, to the call of distress.

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ON THE MANAGEMENT OF THE SPASTIC COLON AND MUCOUS COLOPATHY, ESPECIALLY IN HYPERVAGOTONIC PERSONS.*

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Among the common tasks of the general practitioner is that of the treatment of patients suffering from habitual constipation. The therapy of so-called atonic constipation (better called hypokinetic constipation) presents difficulties enough; but the form of habitual constipation in which there is persistent spasm of the colon (hyperkinetic-dyskinetic constipation), often associated with paroxysms in which larger or smaller quantities of mucus are passed from the bowel (so-called "mucous colopathy" or "myxoneurosis intestinalis") is even more obstinate and more difficult satisfactorily to treat, especially when it occurs in patients of outspoken hypervagotonic constitution. It has occurred to me, therefore, that a discussion of this topic might be of particular interest to this audience, which, as I understand it, is composed largely of physicians in general practice.

The Motility of the Large Intestine. It would seem desirable to preface my remarks by a brief résumé of existing knowledge of the physiology of colonic motility, since a thorough understanding of the mechanisms of this motility under normal conditions is essential for the interpretation of the abnormal states that are encountered when these mechanisms are disturbed.

You will recall that in the large intestine (as well as in the small bowel) contractions of the longitudinal strands of muscle shorten and widen the tube, whereas contractions of the circular muscle narrow the tube. The so-called *pendulum movements* have the function of mixing the food derivatives intimately with the juices secreted by the digestive glands and also of placing all portions of the contents of the bowel in contact with the surface of the mucous membrane in order that absorption may take place. The *peristaltic movements* have the function of propagating the intestinal contents analward; among these are included the so-called "great colon movements" that come three times in the twenty-four hours, cause the translocation of the contents of the colon over considerable distances. In addition to these peristaltic movements that propagate the contents distalward, there occur, as we now know, *antiperistaltic movements* that provide for retrograde transport of the colonic contents, that is to say that drive the contents oralward rather than analward. It is particularly in the cecum and the

* Address delivered in the Practical Lecture Series, New York, Academy of Medicine, December 14, 1928.

ascending colon that these antiperistaltic contractions are prominent. As soon as the contents of the ileum are discharged into the cecum, these antiperistaltic contractions begin; they result in the retention of the contents in the cecum and the ascending colon where they not only favor the thorough mixing of the contents but, through the stagnation produced in this part of the large bowel, provide both for the process of bacterial digestion (which is far more important than was formerly thought) and for the absorption of fluids and dissolved substances with consequent concentration of the feces. It is only after the bacterial digestion and the dehydration of the intestinal contents have occurred that these antiperistaltic movements let up; then through peristaltic movements the contents are shoved on into the transverse colon and, later, into the descending colon. The feces remain normally in the sigmoid until, through the movements of defecation, they are discharged to the outside world. In addition to the contractions of the musculature of the colon just described, the smooth muscle of its walls between such contractions is constantly held in a certain degree of tonus (peristolic contraction).

From Roentgen ray studies, it has been shown that barium ordinarily begins to enter the cecum in from one to two hours after it has been swallowed and that the cecum and ascending colon are filled in from two to six hours, whereas it is some ten to sixteen hours before the descending colon and the sigmoid are filled. All the peristaltic movements are a part of the automatic activity of the colon and appear to be innervated by centrifugal impulses from Auerbach's plexus, which in turn is stimulated both mechanically and chemically from the lumen of the bowel and probably also by hormonal influences from the blood. Auerbach's plexus is further influenced by impulses arriving to it through sympathetic and parasympathetic nerve fibers, the innervation of the proximal colon as far as the junction of the first and second thirds of the transverse colon coming from the vagus and the superior splanchnic, that of the distal colon coming from the lower sacral nerves and the inferior splanchnic. The sympathetic fibers carry mainly impulses that depress motility, the parasympathetic (craniosacral autonomic) mainly impulses that increase motility.

The tonus of the musculature of the intestine is believed to be regulated through a plexus in the peritoneal covering of the colon (serosa plexus) without the intermediation of Auerbach's plexus; craniosacral autonomic impulses favor whereas sympathetic impulses inhibit tonus.

Obviously, then, the motility of the colon is a complex affair, dependent upon an intricate set of neuromuscular mechanisms, which must work together in a coördinated or synergistic way for healthy functioning. It is but little wonder that this motility should be easily disturbed, owing either to alteration of its neuromuscular apparatus or to stimuli impinging upon that apparatus.

In habitual constipation, we may find, on the one hand, hypokinetic states of the musculature ("atonic constipation") or, on the other, hyperkinetic states with dyskinetic disturbances of coördination ("spastic constipation"). In not a few cases, there may be hypokinetic phenomena demonstrable in one part of the colon and hyperkinetic-dyskinetic phenomena in another part.

The Secretory, Digestive, and Absorptive Activity of the Large Intestine. In contrast with the secretion (succus entericus) of the small bowel, that of the large bowel contains but few ferments and but little of any one ferment. The glands of the small bowel secrete erepsin, arginase, nuclease, lipase, various carbohydrate splitting ferments and enterokinase, which activates trypsin; the glands of the large bowel secrete perhaps a little erepsin, but mainly mucus. The secretory function in both the small and the large intestine is regulated by impulses from Meissner's plexus (in the submucosa), which in turn is influenced by reflex and psychic influences that excite or inhibit.

The digestive activity of the large bowel is due mainly to bacterial action upon the food products rather than to the action of ferments derived from the glands. We are now fairly well informed with regard to the bacterial flora of different parts of the intestine in normal children and adults; in the latter, under ordinary diet, the colonic flora consists largely of Bacillus coli and of anaërobic bacteria (Gram negative). Disturbance of this bacterial flora and of bacterial digestion often plays a rôle in the origin of constipation, particularly when there is too much destruction of food residues by the activity of the bacteria, or when because of an abnormal bacterial flora poisons are produced that injure the motor mechanisms.

The absorptive activity of the large bowel is slight in comparison with that of the small intestine, for it is in the latter rather than in the former that the bulk of the soluble products of digestion as well as the digestive juices themselves are absorbed. Still, much water and some diffusible salts are absorbed from the large bowel, particularly from the cecum and the ascending colon where the contents become less fluid before being passed on to the transverse and distal colon.

The Symptoms and Signs of Spastic Colon and of Mucous Colopathy. Since heightened irritability of the neural and muscular mechanisms of the colon frequently exists and leads to spasms, to disturbances of coördination of the colonic contractions, and, often, to increased and perverted activity of the glands that secrete mucus, it will be interesting to examine the conditions under which this heightened irritability occurs, to discover the parts of the large intestine most frequently involved, and to discuss the symptoms and signs that most frequently appear. It would take us too far afield to study all types of disturbance of colonic motility; I shall, therefore, not discuss the hypokinetic form of habitual constipation, except insofar

as hypokinetic disturbances may play a rôle in the clinical picture of the form of constipation that is predominantly spastic. Nor shall I attempt to deal with the intestinal spasms that accompany outspoken inflammatory or ulcerative diseases of the colon, but shall rather limit my remarks to the spastic colon that is either a part of a general nervous hyperexcitability or is a neurosis that is predominantly manifested in a local colonic spasm. In these neurotic states, we have to deal with (1) spasm usually of the distal colon; (2) increased peristalsis and antiperistalsis in the cecum and proximal colon with prolonged stasis there and consequent overconcentration of the contents because of dehydration, and (3) increased production of mucus in the form either of jelly-like masses or of inspissated sheets or tubes of mucus. There is thus a profound disturbance of colonic motility (in the sense of hypermotility [both peristaltic and peristolic] and of incoördination of the colonic contractions) combined with a marked disturbance in the secretion and discharge of mucus.

The *subjective symptoms* vary markedly in different patients. It is often difficult to determine in a given case in how far they are due directly to the spastic constipation and in how far to an underlying psychoneurotic state associated with increased parasympathetic tonus (hypervagotonia). The abdominal pains and discomfort are doubtless attributable to the spasm, but the way the patient reacts to these depends much upon the general state of the nervous system. When severe pains accompany the discharge of mucus or precede or follow this, the condition is spoken of as "colica muçosa." Affective disturbances are frequently met with in association with colonic spasm and may be very pronounced. There is often a change of mood, the patient becoming depressed and anxious during an attack; but it must be borne in mind that, in predisposed persons, fatigue and depression may precipitate an intestinal spastic state, which in turn can accentuate feelings of sadness and exhaustion that are already present.

The pain may be so very severe and may occur with such extreme suddenness as to excite the idea in a physician who hears the complaint that some malady other than mere spasm of the wall of the colon must exist. In such cases, I have known the pain to be regarded by physicians sometimes as that of gall-stone colic, of renal colic, of acute appendicitis, of gastric or duodenal ulcer, or of angina pectoris! I have known morphin to have been administered to relieve these pains and I have seen patients who have been operated on for a supposed condition of primary surgical urgency within the abdomen, though at the laparotomy nothing more than spasm of the colon could be found!

The constipation complained of may be slight in the milder cases or may be so pronounced in the severer cases as to yield the clinical picture of intestinal obstruction (spastic ileus). In most cases, the

stools are frequent but unsatisfactory; the desire for defecation is strong but the accomplishment is meager. Small fragmented and flattened stools may be passed, but the patient feels after the passage that the bowel has not properly emptied itself; there is lack of that feeling of well-being that follows normal defecation. Often after much strain and discomfort only masses or sheets of mucus will be found to have been discharged. Because of the frequent small stools the patients may say that they have both diarrhea and constipation. After sheets of mucus have been passed, soreness in one or another part of the colon may be felt for a day or two.

On *objective examination* of the patient, the spastic portion of the colon can frequently be palpated as a small firm cylinder. This palpable cord may be very tender; frequently, tenderness can be elicited on palpation throughout the whole course of the colon. On proctoscopic examination, often desirable to rule out carcinoma or ulcer, a spasm at the junction of the sigmoid and rectum with rhythmical contractions can sometimes be directly observed.

The *findings on Roentgen ray examination* are very characteristic. A series of roentgenograms made at intervals after the ingestion of barium reveals the site of the spasm (most often in the transverse or descending colon), the hypermotility of the proximal colon and despite this, the ascendens stasis due to antiperistalsis. There are marked differences in the roentgenograms after barium enemas administered before and after the administration of atropin; the spastic contractions obvious in the former are entirely absent in the latter.

In persons of markedly hypervagotonic constitution, signs of increased parasympathetic tonus in domains other than intestinal may become evident. Thus gastric hyperacidity and pylorospasm are frequently observable; bradycardia and cardiac arrhythmias with precocious systoles are also common. One of my patients suffered from recurrent vagotonic heart block with syncopal attacks coincident with some of his paroxysms of mucous colopathy. Dizziness, transient diplopias, slight dysarthrias, and paresthesias in the lower extremities occasionally accompany exacerbations of the colonic spasm.

The malady is often described as a "mucous colitis," but, as a rule, we deal with a motor and secretory neurosis rather than with actual inflammation. A true colitis, may, it is true, be complicated by paroxysms of spasm and of mucous secretion, and in a few cases of the primary neurosis a secondary colitis may be superimposed; in either case, the feces contain an excess of mucus between the attacks, whereas with ordinary uncomplicated spastic and mucous colopathy there is usually no excess of mucus in the stools in the interparoxysmal periods.

Differential Diagnosis. Before deciding upon the diagnosis of a functional disorder, great care should be taken to rule out serious

organic disease. When the mucus is blood-tinged, as it often is, ulcerative processes in the colon or, in older persons, neoplasm may be suspected and should be ruled out by digital exploration of the rectum, by proctosigmoidoscopy, and by roentgenography. Organic stenoses of all sorts are similarly to be eliminated; pericolitic adhesions with partial obstruction are common after gynecologic operations and after operations on the gall bladder or appendix and should always be kept in mind as possible causes of clinical pictures resembling the neurosis under consideration. Reflex spasm secondary to diseases of the gall bladder, the appendix and the genital organs should be watched for. Neurasthenic, psychasthenic, hysterical and hypochondriacal trends speak for intestinal neurosis; but it should never be forgotten that neurotic and psychopathic persons may also harbor organic intraäbdominal disease. It has been my experience, however, to see mistakes made through the assumption of organic disease and through failure to conceive of the symptoms as being possibly due to a neurosis oftener than in the opposite direction. It is these mistakes that have led so often to superfluous abdominal operations.

Treatment of Spastic Colon and Mucous Colopathy. Despite the fact that this malady, uncomplicated, is not dangerous to life, it is responsible for much discomfort, misery and chronic invalidism, and it may be very recalcitrant to treatment. In some cases, fortunately, the response to therapeutic effort is most gratifying, the paroxysms disappearing entirely; in all cases, much can be done to diminish the number and severity of the attacks, provided the patient will adopt the therapeutic measures necessary thereto; but a large number, despite the best treatment known to us, continue to have at least some attacks, especially when subjected to physical, mental or emotional strain. It is not uncommon to meet with relapses after infections, after a bereavement, after familial or other social conflicts, or even after a sudden drop in the Dow Jones averages in Wall Street.

The treatment may be divided into: (1) That of the attacks, and (2) that of the interparoxysmal periods. When an attack is severe, the pain may require immediate relief and for this a dose or two of codein or of pantopon (hypodermically or orally) will usually suffice, especially if the patient will rest quietly in bed, apply heat to the abdomen and in addition, swallow a tablet of atropin (1 mg.) or of novatropin (2½ mg.). A subcutaneous injection of 1 mg. of atropin sulphate may be administered instead of the tablet by mouth if a quick effect is desired. This treatment will often be followed by relaxation of the spasm and disappearance of the pain. Purgatives and colonic irrigations are best avoided though if the constipation has been marked and much mucus appears in the stools, one or two colonic irrigations with warm salt solution to which a little sodium bicarbonate has been added may be beneficial. After the acute

symptoms have subsided, the patient may take belladonna, atropin, bellafolin, or novatropin three times a day for a few days and a small intrarectal injection of warm olive oil may be made at 9 P.M. for a few nights.

After an attack, the treatment should be directed toward the prevention of spasm and constipation, toward combating any complicating catarrh of the colon and toward the overcoming of the underlying general neurosis. This treatment should be planned after the making of a general diagnostic survey that will reveal not only every physical disease existent, but also all faulty habits, any peculiarities of personal make-up and any inimical influences in the familial, economic and social environment. No condition, local or general, that could contribute to the invalidism should be permitted to go overlooked.

Dietotherapy. There has been a clash of opinion as to the best diet for mucocolopaths with spastic colon. Some, following the lead of von Noorden and Lenhartz, have recommended a *coarse diet* (yielding abundant cellulose residue) inclusive of a large fat ration; such a diet would contain large quantities of foods that mechanically and chemically stimulate the large intestine to contraction (brown bread, bran muffins, leafy green vegetables, cabbage, cauliflower, brussels sprouts, vegetable salads, pickles, turnips, radishes, peas, beans, mushrooms, raw and cooked fruits, honey, nuts, figs and raisins). Such a diet, may in certain instances, especially those in which there is hypokinesis of one part of the colon associated with spasm in another part, be found desirable; but for most mucocolopaths with spasm, I have found it distinctly harmful. I prefer with A. Schmidt, Einhorn, Bastedo, Cawadias, Chase and many others, to use a bland protective diet rather than a stimulating diet in these cases, at any rate until the colonic spasm has been well overcome. As one of my colleagues, Dr. Thomas R. Brown, has emphasized, the coarser diet may be suitable for the intestine of Central Europe, but not for the American intestine when spastic, however desirable when it is hypokinetic.

Such a bland diet may contain meat, chicken, fish, milk, eggs, cream, curds, junket, cottage cheese, butter, with moderate amounts of well-cooked cereals, vegetable purées, stewed fruits and simple desserts. A large glass of acidophilus milk may be taken night and morning. Coffee, tea, alcohol, tobacco and condiments should be restricted. Mineral oil to lubricate and agar-agar to fill the intestine are very advantageous, as they do not irritate the bowel. Abundant water drinking before meals is desirable. In the planning of the diet as a whole, due regard should be given to the general state of nutrition, reducing the caloric intake in the obese, increasing it in the undernourished. When a complicating catarrh of the colon is present, the diet may have to be rigidly protective for a time.

Pharmacotherapy. The repeated use of purgatives and long-continued colonic irrigations are, in my opinion, definitely contraindicated. It seems to me probable that future generations will look back upon the vogue of colonic irrigation in our time with amusement similar to ours for the treatment by the black stick *a posteriore!* As long as the spasm of the colon continues, drugs that relax that spasm may be administered with advantage. The most used remedy is belladonna. Ever since Trousseau introduced his famous pill (extracts of leaves and root of belladonna), physicians have given it or tincture of belladonna with benefit to patients suffering from spasm of the colon and the form of constipation that accompanies it. One may, of course, use atropin instead, say 1 mg. tablet on rising and on retiring; or one may give 2 or 3 cg. of bellafolin after each meal. Extract of belladonna may also be given by suppository if desired. Recently, novatropin (homoatropin methylbromide) has come into use as a substitute for atropin in lessening spastic states due to parasympathetic hypertonus; it is said to be some fifty times less toxic than atropin though it equals atropin in the reduction of spasm. It is available in 2½ mg. tablets of which one may be administered on rising and on retiring. For lessening, by drugs, the general hyperirritability of the nervous system, so common in these patients, we may resort temporarily to bromide preparations or to luminal.

Another method of decreasing parasympathetic tonus has lately been introduced. I refer to the administration of Collip's parathyroid hormone along with calcium lactate. Bockus, Bank and Wilkinson have treated a series of 17 patients of mucous colopathy, using about 2 gm. of calcium lactate thrice daily and injecting fifteen units of parathormone (Collip) intramuscularly every third or fourth day. In 12 of the cases there was relief of the local symptoms, and in 10 of the cases the subjective nervous phenomena were lessened. The method would seem worthy of further trial especially in cases that do not respond satisfactorily to treatment with diet and belladonna.

Attention should be paid to the acidity of the gastric contents. When hyperacidity coëxists, a blunting powder should be given after meals; achylia is a less frequently associated phenomenon, but if present, is an indication for hydrochloric acid before meals.

When there is much flatulence (often accompanied by palpitation, precordial anxiety, insomnia and depression), a temporary qualitative change of diet (restriction or removal of carbohydrates) may be advantageous. If the intestinal gases and feces are foul-smelling, due to putrefaction of proteins, the addition of acidophilus milk and stewed fruits will be helpful. Some patients, who complain much of "gas," find relief from magnesium perhydrol (1 teaspoonful in water or 1 or 2 half-gram tablets taken thrice daily). In both fermentative and putrefactive processes in the large bowel, the

powder (introduced by Antoine and Rolland of Paris) containing bismuth carbonate, kaolin, and magnesium hydrate, given over a period of several weeks is asserted to be beneficial.

Gout seems to play a rôle in etiology in some patients; cinchophen or neocinchophen may then be helpful along with reduction of the purin intake.

Physical Therapy. Warm baths and local heat to the abdomen are preferable to any other form of hydrotherapy or thermotherapy. If massage is used, it should be applied to parts other than the abdomen, or, at any rate, great care should be taken to avoid stimulation of a tender spastic colon. Electrotherapy, though much vaunted, is not indispensable; its effects are chiefly due to suggestion Nor do I think any special form of balneotherapy or any particular "spa" necessary, though doubtless many patients will find benefit at a well-conducted watering place where there is careful supervision of the patients as regards both mental and physical hygiene. Training in "progressive voluntary relaxation" can be very helpful as the tension in the voluntary musculature decreases, relaxation of the colonic tonus is favored.

Psychotherapy. Since a large proportion of mucocolopaths are of neurotic constitution, much help can be given by rational and systematic psychotherapy. First of all, the removal of apprehension of the existence of a severe organic disease (such as cancer of the colon, ulcer, or gall-bladder inflammation) by means of a general diagnostic survey that will convince the patient of its accuracy and thoroughness can be most helpful. Again, a discussion of any other fears, worries or strains to which the patient is subject may be advantageous. Close supervision of the mode of life with definite guidance of activities for a time will make many nervous colopaths grateful to their physicians. In severe cases of mucocolopathy associated with outspoken psychoneurotic or mild psychotic states the pathologic process is not restricted to the vegetative nervous system; for such cases a thorough going rest and upbuilding cure, with isolation, away from the patient's home, and with the aid of a special nurse, occupation therapy and psychotherapy may be desirable, even indispensable, for success.

Surgical Therapy. In very obstinate cases, therapeutists with surgical leanings have grown discouraged with nonsurgical therapy and have resorted to exploratory laparotomy in the hope of finding some local cause for the malady; and, finding none, have established an appendicostomy fistula for purpose of irrigation, have resected a part of the colon or removed the whole of it, or have anastomosed the ileum with the sigmoid colon. This lamentable chapter of therapy I dislike to discuss, but I feel it my duty to say that operations of the kind mentioned for uncomplicated spastic colon and mucous colopathy seem to me not only unjustifiable but distinctly reprehensible. The treatment of this functional malady should be

predominantly medical rather than surgical; but it involves not only a knowledge of internal medicine in the narrower sense but also an acquaintance with psychologic and social medicine.

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CHRONIC ADHESIVE PERICARDITIS IN CHILDHOOD.

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The problem of pericarditis in children is an interesting and important phase of the study of rheumatic heart disease. Pericarditis is important because of its frequency and its damaging results. Sir John Broadbent[1] states that at the Children's Hospital in London evidence of pericarditis was present in all but 6 of 100 fatal cases of heart disease (1881–1892). Coombs[2] gives the incidence of pericardial lesions in cases of death due to heart disease at the Bristol General Hospital as follows:

Patients dying in the first decade	100.0 per cent
Patients dying in the second decade	83.3 "
Patients dying in the third decade	41.6 "
Patients dying in the fourth decade	23.0 "
Patients dying after forty years	26.0 "
All patients	53.0 per cent

While acute pericarditis is not difficult to recognize, many mild attacks are overlooked, and the after effects are little understood. The disappearance of a friction rub and the absorption of an effusion do not necessarily mark the end of an attack of pericarditis. The process may, and commonly does, go on to productive changes with the formation of nodules and scar tissue,[3] resulting in adhesions which may obliterate the pericardial cavity and bind the heart to the surrounding structures. In this connection, two questions are of special interest: (1) to what extent do the processes started by an attack of pericarditis handicap a child who survives the acute attack? (2) How often does an attack of pericarditis result in adhesions which can be recognized clinically?

In 1898, Sir John Broadbent[4] said that the key to the solution of the problem of adherent pericardium seemed to lie in the investigation of cases of pericarditis which could be kept under observation while going on the formation of adhesions.

The present study* is an attempt to follow, over as long a period as possible, 51 children who have had acute pericarditis or in whom a tentative diagnosis of adherent pericardium has been made. The cases were taken as they came without any attempt at selection, all those children who were known to have a pericardial effusion or friction rub and all those who presented signs suggesting adherent pericardium. The only cases omitted were those who were seen but once in the Clinic and those who were never followed after discharge from the ward. Some of the children have been under observation for a relatively short period; others have attended the Clinic for ten years; many have been admitted to the hospital, not once, but repeatedly; most of them have spent months in convalescent homes; a few have been lost.

The study is obviously incomplete in many ways. It cannot include all those children who have had pericarditis, for it is often impossible to obtain an accurate history; friction rubs are often transitory and pericardial effusions may be described as "pleurisy," "heart trouble," "pneumonia" or "water on the chest." In many cases it is impossible to follow patients over a long period of years. Finally, it is difficult to interpret physical signs, and it is usually impossible to check clinical findings with postmortem records.

Fifty-one children are included in the present study. In 39 of the cases there is a definite record of some pericardial involvement. In 2 of these cases, both of which lacked history of an attack of acute pericarditis, complete obliteration of the pericardial sac with extensive adhesions was found at autopsy; in one a tentative diagnosis of adherent pericardium was made during life; in the other the autopsy finding was quite unexpected. In the remaining 11

* This study is based upon the records of the First Medical Division and the Children's Cardiac Clinic of the New York Hospital. Services of Dr. Lewis A. Conner and Dr. Joseph C. Roper.

cases a tentative diagnosis of adherent pericardium was made on the basis of signs and symptoms. Twenty-two cases are under observation at the present time, 21 have died (with 5 autopsies) and 8 have been lost. Before discussing the course of the disease or the physical signs, it is convenient to summarize the acute outbreaks in each child's history. No child who died during an acute attack of pericarditis is included in this series; these are all children who are alive at present or who died after the acute process had subsided. An attempt has been made to include information as to the valvular damage, indicating the lesion diagnosed by initials (M. for mitral, A. for aortic, I. for insufficiency, S. for stenosis) and to give the condition of the child when last seen. Unless otherwise noted, as dead or lost, the children are under observation at the present time.

TABULATION OF CASES.

1. Augustine A.:
   - 11 years, mild rheumatism.
   - 13 " *pericarditis with effusion;* M.S.
   - 16 " rheumatic fever; A.I. and possibly M.S.
   - 17 " rheumatic fever; A.I., M.S. and adhesive pericarditis; condition poor; dyspnea, tachycardia and cyanosis. Died.
2. Salvatore B.:
   - 6 years, dyspnea and palpitation.
   - 7 " *pericarditis with effusion;* M.S.; died 3 months later.
3. Harry B.:
   - 5 years, said to have "heart trouble."
   - 6 " tonsillectomy for frequent sore throats.
   - 7 " rheumatic fever (2 attacks); precordial pain; M.S.
   - 10 " *pericarditis with effusion.*
   - 13 " occasional joint pains for 3 years; improving.
4. Thomas B.:
   - 4 years, "fever;" M.S.
   - 7 " *pericarditis with effusion;* large heart and liver.
   - 8 " died.
5. David C.:
   - 5 years, rheumatic fever for 2 months; growing pains for next 3 years; scarlet fever (exact age unknown).
   - 8 " rheumatic fever for 4 months; "heart trouble."
   - 10 " rheumatic fever.
   - 12 " tonsillitis; rheumatic fever; *pericarditis with effusion;* M.S. and A.I.
   - 13 " purpura or erythema; febrile attacks.
   - 14 " auricular fibrillation and cardiac decompensation.
   - 15 " three febrile attacks; died.

5*a*. Jimmy C.:
   - 7 years, rheumatic fever.
   - 9 " dyspnea.
   - 10 " dyspnea, little edema, large liver; M.I. and M.S.; *pericardial friction rub.*
   - 11 " very large liver, ascites; M.S. and A.I.
   - 12 " died.

6. Margaret C.:
   5 years, chorea.
   7 " chorea; tonsillectomy; M.I.
   9 " chorea.
   11 " chorea; *pericarditis with effusion;* nodules; M.I.
   12 " chorea; nodules; M.I. and A.I.
   14 " chorea.

8. James D.:
   12 years, indefinite history of growing pains; tonsillectomy; M.S.
   13 " ascites; large liver; M.S. and A.I.
   14 " died.

9. Armande de R.:
   7 years, sore throats; vague pains; tonsillectomy.
   8 " chorea; pleurisy (or pericarditis?) with effusion.
   10 " M.S., signs of adhesive pericarditis; condition poor and growing worse.

10. Santos, D.:
   6 years, scarlet fever followed by joint pains and tachycardia; *pericardial friction rub;* M.I.
   7 " M.S. and A.I.
   8 " condition rather poor.

11. Agnes E.:
   6 years, acute appendicitis with appendectomy and drainage; 3 months later tachycardia and cough; large heart; M.S.
   8 " cardiac decompensation; probably adhesive pericarditis. Died, February, 1929, apparently of cardiac failure.

12. Edward E.:
   8 years, joint pains; *pericarditis with effusion;* M.S.
   10 " two mild rheumatic attacks.
   22 " in good health; M.S.

13. Edward F.:
   4 years, tonsillectomy.
   10 " abdominal pain ("chronic appendicitis"), M.I. Six months later rheumatic fever, M.I. and possibly M.S.
   12 " *pericarditis with effusion;* M.S. and possibly A. I. Died 3 months later (autopsy).

14. Morris F.:
   10 years, rheumatism and "heart trouble."
   15 " *pericarditis with effusion;* in good condition 6 months later. Lost.

15. Veronica F.:
   10 years, chorea.
   11 " "heart trouble."
   12 " growing pains, "heart trouble," in bed 9 months; M.S.
   14 " growing pains; bronchopneumonia; M.S. and possible A.I., adhesive pericarditis.

16. Sidney G.:
   10 years, history of frequent rheumatic and abdominal pains.
   11 " nodules; M.S. and A.I.
   12 " growing pains, abdominal pain.
   14 " growing pains; rheumatic fever.
   15 " rheumatic fever; M.S. and A.I., adhesive pericarditis.(?)

17. Frank G.:
    8 years, rheumatic fever.
    9 " *pericarditis with effusion* for 6 weeks; tonsillectomy.
    12 " pleurisy with effusion; M.I. and A.I.
    15 " *pericarditis with effusion* for 6 weeks.
    16 " fever, *pericardial friction rub.*
    17 " *pericarditis with effusion* for 1 month.
    20 " well and working.
    This boy has recently developed a subacute bacterial endocarditis with Streptococcus viridans in his blood. Died.
18. Jeanette K.:
    6 years, scarlet fever.
    7 " sore throats, muscle pains, tonsillectomy.
    8 " rheumatism, *pericarditis with effusion;* possible M.S. Six months later enormous heart, cardiac failure, M.S.
    10 " large heart and liver, auricular fibrillation; died.
19. Rita K.:
    7 years, *pericarditis with effusion;* fever for 18 months; M.S.
    8 " nodules; M.S. and possibly A.I.
    9 " large heart and liver, ascites, decompensation.
    10 " no ascites, fair compensation.
    11 " decompensation and ascites; M.S. and A.I., improvement with rest and digitalis.
    12 " Died, March, 1929, of cardiac failure and terminal bronchopneumonia. Auricular fibrillation was present for the last three weeks of life.
20. Ida K.:
    10 years, "heart trouble" for 3 years, *pericardial friction rub;* M.S. and M.I., enormous liver, ascites.
    11 " no ascites, signs of adhesive pericarditis.
    13 " died very suddenly after 2 weeks of moderate cardiac decompensation.
21. Annie K.:
    4 years, rheumatism.
    5 " rheumatism, "heart trouble."
    6 " rheumatism, measles.
    7 " *pericardial rub and effusion;* M.S. and M.I., muscle pains, nodules and protracted fever.
22. Bernard L.:
    7 years, chorea (history of measles, pleurisy and pneumonia).
    8 " rheumatic fever, pneumonia, *pericardial friction rub;* M.S.
    9 " rheumatic fever.
    10 " growing pains.
    11 " rheumatic fever; M.S.
23. Edward L.:
    5 years, "grippe" followed by joint and muscle pains.
    6 " "heart trouble."
    7 " *pericarditis with effusion.*
    8 " pain in left chest.
    9 " poor condition, large overacting heart. Lost.
24. Anna M.:
    7 years, scarlet fever.
    9 " tonsillitis.
    11 " rheumatism followed by "pleurisy" with cough and dyspnea.
    13 " *pericardial friction rub;* A.I. and A.S.
    14 " tonsillectomy. Lost.

25. Henry M.:
    10 years, tonsillitis; precordial pain; M.S.
    12 " rheumatism; nodules.
    13 " erythema multiforme; signs of adherent pericardium.
    15 " occasional rheumatic pains.
26. Paul M.:
    16 years, sore throat; rheumatism; pericardial friction rub; M.S.
    17 " in good condition. Lost.
27. Joseph Mo.:
    10 years, cardiac pain and dyspnea; in bed for 1 year.
    11 " cardiac pain and dyspnea; in bed for 2 weeks.
    13 " cardiac pain and dyspnea; in bed for 4 months.
    15 " cardiac decompensation with edema and dyspnea; venous thromboses; M.I., M.S., A.I. Died (autopsy).
28. Joseph Mu.:
    8 years, tonsillitis; scarlet fever; normal heart.
    11 " rheumatic fever.
    14 " rheumatic fever followed by dyspnea and tachycardia.
    15 " *pericardial friction rub and possible effusion;* M.S. and A.I.; in good health six months later.
29. Doris O.:
    3 years, rheumatic fever.
    4 " rheumatic fever.
    5 " rheumatic fever.
    6 " rheumatic fever; M.S.
    7 " *pericarditis with effusion.*
    8 " "acute myocarditis;" pericardial friction rub.
    9 " tonsillectomy.
    11 " rheumatic fever.
30. Helen P.:
    9 years, rheumatism; tonsillectomy; M.S. and M.I.
    10 " rheumatism; *pericardial friction rub;* M.S. and A.I.
    11 " acute bronchitis; *possible pericarditis with effusion.*
    12 " *pericardial friction rub;* enormous heart.
    14 " Died.
31. Sylvia P.:
    3 years, rheumatism; M.I.
    4 " otitis media; growing pains.
    5 " rheumatism; *pericardial friction rub;* M.I. and possibly M.S.
    6 " *pericarditis with effusion;* pertussis.
    7 " rheumatism; 6 months later fever, tachycardia, *pericardial friction rub* and cardiac failure with general anasarca. Died (autopsy).
32. Rocco P.:
    3 years, pneumonia.
    4 " *pericardial friction rub;* M.S.; died a few months later.
33. Rosa R.:
    12 years, *pericarditis with effusion;* large heart; no murmurs.
    13 " good health; A.I. Lost.
34. Rosie R.:
    4 years, "stomach trouble" with large heart, liver and spleen; M.I.
    5 " died with general edema.
35. Joseph R.:
    8 years, rheumatism; large heart; *pericardial friction rub;* M.I.
    9 " enormous heart; M.I. and possibly A.I.
    10 " died.

36. Helen R.:
    5 years, abdominal pain, malaise and dyspnea; 6 months later increased dyspnea, large heart and liver; M.S. and A.I.
    6 " dyspnea; *pericardial friction rub;* later ascites, edema, auricular fibrillation. Died (autopsy).

37. Isadore R.:
    7 years, tonsillitis.
    8–9 " tonsillitis, vague pains.
    12 " rheumatic fever.
    13 " *pericardial friction rub;* M.I.
    15 " tonsillectomy; heart not enlarged, systolic murmur. Lost.

38. Louis R.:
    6 years, torticollis; frequent sore throats.
    9 " tonsillectomy.
    14 " *pericarditis with effusion;* M.S. and A.I.
    19 " in good health.

39. Miriam S.:
    3–(?) years, joint pains, nodules, scarlet fever (exact age unknown).
    14 " pericardial friction rub; large heart and liver; M.S. and A.I. Died.

40. Paul S.:
    6 years, tonsillectomy.
    7 " rheumatism.
    8 " rheumatism; nodules; M.S. and adhesive pericarditis; swollen liver.

41. Nettie S.:
    3–10 " frequent tonsillitis and vague pains; tonsillectomy.
    9 " fever for a few days.
    11 " "said to have a weak heart."
    13 " pericardial friction rub; dyspnea and tachycardia; M.S.

42. Michellina S.:
    4 years, *pericarditis with effusion;* later bronchopneumonia.
    5 " M.S.
    6 " M.S.

43. Hazel S.:
    4 years, rheumatic fever.
    7 " influenza.
    11 " tachycardia; large heart; M.S.; pertussis.
    13 " onset of auricular fibrillation.
    17 " very large heart with dilated left auricle.

44. Julius T.:
    6 years, tonsillectomy for frequent sore throats.
    7 " bronchitis; M.I. and A.I.
    8 " otitis media; occasional rheumatic pains.
    10 " *pericarditis with effusion;* A.I. and possibly M.S.
    14 " severe rheumatic fever; A.I.

45. Arthur T.:
    8 " said to have "heart trouble."
    12 " occasional fever and precordial pain, dyspnea; M.S. and M.I.
    13 " fever; tonsillectomy.
    18 " acute cardiac decompensation; flutter and fibrillation. Died (autopsy).

46. Andrew T.:
    3 years, rheumatism.
    4 " cough and nausea for 3 months.
    7 " nosebleeds.
    14 " fever; A.I.
    16 " signs suggesting adhesive pericarditis.
47. Dominick T.:
    11 years, diphtheria.
    12 " rheumatic fever; M.S. and A.I.; six months later *pericarditis with effusion.*
    13 " died.
48. Fred V.
    8 years, chorea.
    14 " chorea.
    15 " large heart; possible adhesive pericarditis; M.S. Lost.
49. William W.:
    ? years, grippe, measles, growing pains, scarlet fever.
    8 " tonsillectomy.
    15 " *pericarditis with effusion;* nodules; A.I.
    16 " very large heart.
    18 " living; unable to attend Clinic.
50. Frederick W.:
    ?–12 years, repeated attacks of chorea, tonsillitis and rheumatism.
    13 " tonsillectomy; M.I. and A.I.
    17 " *pericarditis with effusion;* M.S. and A.I. Lost.

Clinical Course. In reviewing these cases several important facts stand out. The rheumatic infection usually appeared at an early age, and in the majority of cases was characterized by repeated acute attacks. In some cases the exact age of onset is unknown, because a child at the time of the first examination was found to have definite signs of mitral stenosis but no history which could be interpreted as evidence of rheumatism. In other cases, the history obtained from the parents was indefinite, and it seemed probable that "growing pains" had been present for some time before attention was called to the child's sickness. The exact age at which the rheumatic infection first appeared is often unknown, but the infection was present at, or before:

Years.	Cases.
3	6
4	5
5	5
6	5
7	8
8	6
9	2
10	6
11	2
12	4
After 12	1

In addition to the more acute manifestations of the disease, many of the children had mild growing pains and occasional periods of low-grade fever of which accurate record is usually lacking. The

early appearance and the severity of the infection are important because it is in the severe infections that pericarditis is most common and also that the heart is most damaged. In considering the prognosis and the course of the disease one should be able to differentiate between the results of pericarditis and those of infection elsewhere, but unfortunately this is rarely possible.

In 26 cases, an attack of pericarditis seemed to be a definite turning point, the beginning of a train of unfavorable signs and symptoms which became progressively worse and which usually led to death within a short time. Only 1 child in this group is known to be alive for more than three years after the acute attack; 19 are dead and 7 are growing worse.

Of the 21 who died, all had symptoms and signs of cardiac insufficiency. In practically every case the apparent cause of death was cardiac failure; often the exact cause could not be determined. One patient died of pneumococcus endocarditis and septicemia, 1 of bronchopneumonia, 1 during an attack of acute rheumatic fever, and 1 died suddenly. In each of these cases, there was marked cardiac decompensation before death. In all the other cases, death was ascribed to the cardiac condition, but in no case could it be said that the pericarditis was directly responsible. In 5 of these cases, there was no definite record of acute pericarditis, but, in 4 of these, there was a history of an acute illness which was probably pericarditis and a tentative diagnosis of adherent pericardium was made during life, and in one case was confirmed postmortem. In the fifth case in which there was no history of pericarditis, complete obliteration of the pericardial sac was an unexpected autopsy finding. In the remaining cases, death followed the acute attack after an interval of from three months to three years. These cases with the associated valvular lesions and evidences of myocardial damage are summarized in Table I.

These were all children who "recovered" from acute pericarditis, but they were never well. Clinically they showed evidence of continued infection and progressive cardiac damage; fever, tachycardia, pain, leukocytosis, dyspnea, weakness and edema in varying degrees. All of them had evidence of endocardial damage, signs of mitral stenosis in every case, of aortic insufficiency as well in 12 cases, and of mitral stenosis, aortic insufficiency and stenosis, and tricuspid stenosis in 1 case. In every case there were symptoms of cardiac failure, and in all but 5 cases, in which the records are incomplete, there were signs of myocardial damage. (See Table I.) These signs consisted of abnormal electrocardiograms or of microscopic changes demonstrated at autopsy. The abnormal electrocardiographic signs were abnormalities of the *T* wave, low voltage, and widening, notching and slurring of the *Q-R-S* group. The 5 cases which came to autopsy showed complete obliteration of the pericardial sac and adhesions to the surrounding structures. In 4 of

these, the diagnosis was made before death. It has been said that adherent pericardium is regarded as the usual cause of cardiac failure in rheumatic children,[5] but from these few cases it would appear that a severe and protracted infection with a pancarditis was at least as important as interference with the work of the heart due directly to the adhesions.

TABLE I.

Case No.	Name.	Age at death, yrs.	Time before death at which pericarditis was noted.	Valvular lesion.	Evidence of myocardial damage.
1	Augustine A.	17	4 yrs.	M.S. and A.I.	EKG.
2	Salvatore B.	7	3 mos.	M.S. ?	
4	Thomas B.	8	1 yr.	M.S.	
5	David C.	15	3 yrs.	M.S. and A.I.	Fibrillation; EKG.
5a	Jimmy C.	12	2 yrs.	M.S. and A.I.	EKG.
8	James D.	14	?	M.A. and A.I.	EKG.
11	Agnes E.	8	2 yrs. ?	M.S.	
13	Edward F.	12	3 mos.	M.S. and A.I.	EKG.; autopsy.
17	Frank G.	20	11 yrs.	M.I. and A.I.	EKG.
18	Jeanette K.	10	2 yrs.	M.S.	Fibrillation.
19	Rita K.	12	5 yrs.	M.S. and poss. A.I.	
20	Ida K.	13	3 yrs.	M.S.	EKG.
27	Joseph Mo.	15	3 yrs. ?	M.S., T.S., A.I. and A.S.	EKG.; autopsy.
30	Helen P.	14	2 yrs.	M.S. and A.I.	EKG.
32	Rocco P.	5	Few mos.	M.S.	
34	Rosie R.	5	?	M.I.	
35	Joseph R.	10	2 yrs.	M.S. and A.I.	Autopsy.
39	Miriam S.	14	3 mos.	M.I. and M.S.	EKG.
45	Arthur T.	18	?	M.S. (A.I.)	EKG.; autopsy.
47	Dominick T.	13	6 mos.	M.S. and A.I.	
31	Sylvia P.	7	18 mos.	M.S.	EKG.; autopsy.

Seven children who are still living have become progressively worse following an attack of pericarditis. These cases are summarized in Table II and are similar to those discussed above except for the fact that they are still alive. In passing, it may be noted that the longest interval following the pericarditis in these cases is less than four years.

TABLE II.—LIVING CASES THAT HAVE BECOME PROGRESSIVELY WORSE.

Name.	Age, yrs.	Pericarditis at age of, yrs.	Valvular lesions.	Electrocardiogram.
Santos D.	7	6	M.S. and A.I.	Abnormal.
Armande de R. . . .	10	8 ?	M.S. and A.I.	Abnormal.
Doris O.	11	7	M.S.	Abnormal.
Annie K.	7	7	M.S.	Abnormal.
Michellina S. . . .	6	4	M.S.	Abnormal.
Paul S.	8	?	M.S.	Abnormal.
William W.	18	15	A.I.	?

Twenty-four cases remain to be considered. Of these 8 were lost within two years. When last seen, 2 were in poor condition and were steadily growing worse, 2 were in fair shape, and the remaining 4 were in good health and living reasonably normal lives.

Two boys are in really good health and are working as clerk, fourteen (Edward E.) and five (Louis R.) years respectively, after a severe attack of pericarditis with effusion. One of these boys had two very mild attacks of rheumatism, the other has not been sick since he had pericarditis. Both have valvular lesions, mitral stenosis in one case, and mitral stenosis and aortic insufficiency in the other. The one who has been examined recently has no physical signs which would suggest the presence of adherent pericardium. One other boy (Frank G.) has been in fairly good condition and is working as draftsman in spite of the fact that he has had three severe attacks of pericarditis with effusion, the first eleven and the last three years ago. He has a large heart with the classic signs of aortic insufficiency, but no evidence of adherent pericardium. Very recently there has appeared evidence of subacute bacterial endocarditis. Two younger boys are in fair condition and seem to be improving. One (Andrew T.) has signs which might be interpreted as due to adherent pericardium; the other (Harry B.) had an effusion three years ago, but at the present time has no signs to suggest adherent pericardium. One girl (Hazel S.), who is believed to have an adherent pericardium, is living an active life in spite of the fact that she has had auricular fibrillation for three years and that she has a heart so large that it practically fills her chest. She has not had frequent rheumatic attacks.

Finally, there are 10 children who are in rather poor condition, who have had repeated attacks of rheumatic fever or chorea—in every case at least one attack within the past year—and who all have some evidence of pericardial involvement. The future of these children seems doubtful.

The following table summarizes the fate of these 51 children as far as it is known. While conclusions based upon the observation of such a small series of cases are worthless for statistical purposes, the observations indicate that rheumatic pericarditis in children is a very serious thing and that even with recovery from the acute attack, the prognosis is bad.

TABLE III.—PROGRESS OF 51 CASES OF ADHESIVE PERICARDITIS.

	No.
Patients dead within 4 yrs.	21
Patients growing progressively worse (6 mos. to 3¼ yrs.)	7
Patients living reasonably normal lives	6
Patients in poor condition whose future seems doubtful	9
Patients lost	8
Total	51

Complications. *Ascites.* Twelve patients in this series had marked ascites and enlargement of the liver, but in only 2 cases was the accumulation of liquid so great as to require repeated tapping. In each case the ascites was associated with cardiac decompensation, and in only one case did it seem out of proportion to other evidences of cardiac failure. The important features of Pick's disease or polyserositis are enlargement of the liver, ascites, slight jaundice, weakness and dyspnea; special cardiac symptoms are lacking, but obliterative pericarditis is present. In the cases collected by Pick[6] and by Cabot[7] the ascites lasted for several years, marked cardiac enlargement was usually lacking and the pericarditis was either tuberculous or of unknown etiology. In the cases in this series the ascites and enlargement of the liver may have been of a similar nature, but the picture was that of cardiac failure rather than that of cirrhosis or pseudocirrhosis of the liver. The appearance of ascites in these cases was of more serious import than in the cases collected by Cabot.

Auricular Fibrillation. Auricular fibrillation was observed in 6 of the children in this series. In 4 cases, it appeared as part of a general breakdown preceding death; in 1 case, it was temporary, and the patient subsequently lived with a sinus rhythm for two years; in 1 case it has been present for the past four years. In 2 cases, an attempt was made to restore sinus rhythm by the use of quinidin; both attempts were unsuccessful, although in 1 case the change occurred, but lasted for a few hours only. In 1 case, the fibrillation appeared only after digitalis had been given to a patient with flutter. The diagnosis of mitral stenosis was made in all these cases, and in one that of aortic insufficiency as well. In 2 cases obliterative pericarditis was demonstrated at autopsy.

TABLE IV.—AURICULAR FIBRILLATION IN ADHESIVE PERICARDITIS.

Name.	Age, yrs.	Duration of A.F.	Age at onset of pericarditis, yrs.
David C.	Died at 15	1 yr.	12
Jeanette K.	Died at 10	Few wks.	8
Ida K.	Died at 12	2 wks. (at 10 yrs.)	10
Helen R.	Died at 6	3 wks.	5 (autopsy)
Hazel S.	Living at 17	4 yrs.	?
Arthur T.	Died at 18	2 mos. (flutter)	? (autopsy)

Bacterial Endocarditis. Bacterial endocarditis was present in 2 cases. In one, the infecting organism was a Group IV pneumococcus and the course was acute; in the other, a Streptococcus viridans was present on blood culture and the patient is running the course of a case of subacute bacterial endocarditis.

Physical Signs. It is said that the diagnosis of adherent pericardium is more often missed than made,[8] and that of all important conditions adherent pericardium is the one most likely to come to the

autopsy table undiagnosed.[9] The reasons for this are several. In the first place, adhesions between the two layers of the pericardium may give no symptoms and no signs. In the second place, even when there are adhesions to the surrounding structures, there is no single pathognomonic sign, and every sign considered typical of this condition has been found in the absence of any pericardial involvement. It is commonly said that even though distinctive signs be lacking, the condition is to be suspected when there is a history of acute pericarditis or when the evidence of cardiac failure seems out of proportion to the amount of valvular damage. The group of patients with symptoms of failure out of proportion to the signs is hard to identify in children, and seems to consist of those who have fever and other evidence of active infection and those in whom the cardiac failure is a terminal condition. Every child with rheumatic pericarditis is almost certain to have endocarditis and myocarditis as well, and it is difficult if not impossible to estimate the importance of the pericarditis in any single case.

The physical signs are numerous, but fall into several groups: fixation of the apex impulse and of the outline of cardiac dullness, abnormal systolic retractions produced by the pull of the heart on the surrounding structures, interference with the normal respiratory movements because of adhesions to the diaphragm or the ribs, variations in the arterial or venous pulse, and modifications of the heart sounds. These signs vary with the position, extent and density of the adhesions, and in children are modified by the elasticity of the chests.

In discussing physical signs only those (24) cases will be considered in detail which have been under observation in the Clinic since the present study was started. In the past two years all physical examinations made in the Clinic have been made with the possibility of adherent pericardium specially in mind; all children have been examined repeatedly; and in as many cases as possible confirmatory evidence has been sought in Roentgen ray and electrocardiographic studies.

The first and most striking thing in reviewing these cases is that with few exceptions the children are in poor condition; usually they are in Class II–B* with longer or shorter periods in Class III.* They are children who are never very well and who are often very sick, but the health over a period of years does not seem to be directly related to the severity of the acute attack of pericarditis. Second, almost without exception they are children with very large hearts. In most cases the apex is in the fifth, sixth or seventh space at or near the anterior axillary line, and there is some enlargement to the right as well. With such large hearts, it is not easy to detect by physical examination such signs as lack of change in the cardiac dullness

* Nomenclature for cardiac diagnosis approved by the American Heart Association.

upon respiration or fixation of the apex impulse on change of position. In almost every case, the heart seemed to shift its position to some extent, and usually this shift could be demonstrated by fluoroscopic examination. With elastic chests, however, some shifting might occur even with extensive adhesions. Electrocardiograms taken in three positions have not seemed of definite value,[10,11] in some cases they indicated that the heart was freely movable, in others that it was fixed. In one case in which there was electrocardiographic evidence of a movable mediastinum autopsy revealed obliteration of the pericardial cavity and adhesions to all the surrounding structures. In another case, the electrocardiogram indicated that the heart was fixed, a finding which was confirmed at autopsy.

Systolic retractions of the interspaces alone are common and without significance, being present when a large heart is in direct contact with the chest wall without the usual intervening pad of lung. Systolic retractions of the sternum and costal cartilages or of the eleventh and twelfth spaces in the posterior axillary line are usually caused by adhesions between the heart and the chest wall or between the heart and the diaphragm.[1] Retraction of the costal cartilages and sternum was present in 14 out of 24 cases, and in 6 of these retraction was noted posteriorly as well. Adhesions between the heart and the diaphragm may cause interference with the normal respiratory movements,[12] detected with the help of the fluoroscope or noted as a drawing-in of the epigastrium on inspiration.

Diastolic collapse and abnormal filling of the neck veins are of very doubtful significance. Pulsus paradoxus, present on quiet respiration, is a suggestive sign,[13] and a sign which may be present on one examination but not on the next. Dilated veins over the front of the chest seem to be relatively common, and are probably caused by some interference with the venous return. In general the character of the pulse depends less upon the presence of adherent pericardium than upon other factors such as the predominant valvular lesion.

Pericardial adhesions can, by drawing on different parts of the heart, modify the heart sounds or cause murmurs which may simulate those of any valvular lesion. In this group of children a third heart sound was not uncommon, and when present was usually associated with a palpable shock. In no case did this seem to be an outstanding feature, and even if it had been it would not necessarily have pointed to the presence of pericardial adhesions, as an exaggerated sound and shock are said to be common in three conditions—mitral stenosis, aortic insufficiency and adherent pericardium.[14,15,16] The murmurs heard were interpreted as the result of valvular damage, but when a murmur appeared following an attack of pericarditis, the question arose whether this murmur represented new damage to the endocardium or whether it was related to the peri-

carditis. In 4 patients, all of them young children, signs of mitral stenosis appeared within a short time after pericarditis with effusion,

TABLE V.—ANALYSIS OF PHYSICAL SIGNS OF 24 CASES OF PERICARDITIS

Interval between pericarditis and most recent examination	4 yrs.	3 yrs.	3 yrs.	2 (?) yrs.	1 yr.	2 (?) yrs.	3 yrs.	3, 5, 11 yrs.	3 yrs.	?	6 mos.	4 yrs.	18 mos.	6 mos.	2 yrs.	?	?	?	3 (?) yrs.	4 yrs.	?	5 mos.	3 yrs.	5 yrs.	Total positive.
History of acute pericarditis	*	*	*	?	*	–	*	*	–	–	*	*	*	*	–	–	–	–	–	*	–	*	*	*	14
Increased size of heart	*	–	*	*	*	*	*	*	–	*	*	*	*	*	*	–	*	–	*	*	*	*	*	–	22
Systematic retraction:																									
Anterior	*	–	*	*	–	*	*	–	*	*	–	–	*	–	*	*	–	*	*	–	*	–	*	–	14
Posterior	–	–	*	*	–	*	–	–	–	*	–	–	–	–	*	–	–	–	*	–	–	–	*	–	6
Fixation of heart	*	–	*	?	–	–	–	–	*	–	*	–	*	–	*	*	*	–	*	?	–	–	–	–	9
Interference with respiration	–	–	–	*	–	*	–	–	–	–	–	–	–	–	*	*	–	–	*	–	–	–	*	–	6
Pulsus paradoxus	–	–	–	*	–	*	–	–	–	–	–	–	*	–	–	*	–	–	*	–	–	–	–	–	5
Dilated veins	–	*	*	*	*	*	*	–	–	–	–	*	–	–	–	*	–	–	*	–	–	–	*	–	10

* indicates present. – indicates absent.

Reading across, one sees how often each sign was present; reading up and down, one sees which combinations of signs were present in individual cases.

but this does not mean that the presystolic murmur was caused by the pericarditis:

Armande deR.: Pericarditis with effusion (?) at 8 years; signs of adherent pericardium and of M.S. at 9 years.

Santos D.: Pericardial rub at 6 years; signs of M.S. at 7 years.

Jeanette K.: Pericardial effusion and possible M.S. at 8 years; definite signs of M.S. 6 months later.

Michellina S.: Pericarditis with effusion at 4 years; signs of M.S. at 5 years.

Adherent pericardium may, in the absence of aortic insufficiency, cause a high-pitched, early diastolic murmur, heard at the aortic area and transmitted down the sternum toward the apex. In one case in this series such a murmur was present together with water-hammer pulse, Duroziez murmur and capillary pulse. At autopsy, a normal aortic valve was found and the clinical diagnosis of aortic insufficiency was changed to a postmortem diagnosis of adherent pericardium.[17] In 4 cases in the series the clinical diagnosis was confirmed, and both aortic insufficiency and adherent pericardium were found at autopsy. In 7 of the other 16 cases presenting an "aortic diastolic murmur" this murmur appeared following an attack of pericarditis and might be caused by pericardial adhesions or by disease of the aortic valve:

Augustine A.: At 13 years had acute pericarditis with effusion and signs of M.S.; at 17 years had signs of A.I., adhesive pericarditis and M.S. Died.

Jimmy C.: At 10 years had pericardial rub and signs of M.S.; at 11 years signs of M.S. and A.I.; died at 12 years; no autopsy.

Margaret C.: At 11 years had pericarditis with effusion, signs of M.I.; at 13 years has signs of A.I.

Frank G.: Had pericarditis with effusion at 9, 15 and 17 years; signs of A.I. from 12 years; died at 20 years.

Rita K.: At 7 years had pericarditis with effusion and signs of M.S.; at 8 years had signs of M.S. and possibly A.I.; at 12 years had signs of M.S., A.I. and adhesive pericarditis. Died.

Anna M.: At 11 years had "pleurisy;" at 13 years had signs of A.I. Lost.

Rosa R.: At 12 years had pericarditis with effusion, no murmurs; at 13 years had signs of A.I. Lost.

Summary. From a study of pericarditis in fifty children with rheumatic heart disease the following statements seem justified:

Rheumatic pericarditis appears in association with a severe infection and one which appears early in life. The prognosis is bad; more than one-third of those children who recover from the acute attack are likely to die within three years; probably one-half will die within five years; few will ever lead normal lives.

Pericarditis is associated with valvular disease, usually with mitral stenosis, often with aortic insufficiency, and is usually merely one part of progressive heart disease.

Marked cardiac enlargement is the rule; auricular fibrillation may be present. Ascites appears as part of a general breakdown, and when present presents a somewhat different picture from that described as Pick's disease.

Some physical signs are likely to be present except in those cases where there is little enlargement of the heart and where the general health is unimpaired. These signs may appear within a few months following an acute attack of pericarditis, but their absence does not necessarily exclude the presence of chronic adhesive pericarditis.

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SODIUM RICINOLEATE IN ALLERGIC DISEASE OF THE INTESTINAL TRACT.

Preliminary Report.

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For the last year and a half one of us (M.) has been treating patients with intestinal symptoms, associated with hypersensitization to intradermal injections of heat-killed intestinal bacteria, by the daily administration of castor oil. The theory on which the castor oil has been used is based on the fact, first demonstrated by Larson, that sodium ricinoleate is capable of neutralizing bacterial poisons. Our patients presented many symptoms suggesting an intoxication (the so-called "intestinal autointoxication"), and we were failing frequently to give them relief. As oils are converted into soaps in the intestines, we felt that there was a possibility that bacterial poisons, if present, might be neutralized by the ricinoleates formed in the intestines. Our clinical results, which will be reported shortly, lend support to our theory.

More recently, we have had prepared capsules of sodium ricinoleate which we have employed in similar cases. It has been observed that some of our patients, after prolonged daily use of castor oil, tolerate doses of vaccine considerably larger than can be given usually, without reaction. Vaccines which produce marked local reaction may be detoxified by the addition of sodium ricinoleate (D.), so that little or no reaction follows intradermal injection. If

this reaction occurs in the test tube it is quite possible that dead bacteria in the intestines may be similarly detoxified, furnishing a local antigen, which may, in turn, aid in desensitization.

Clinically, it has been observed, in patients with evidence of allergy of intestinal origin, that there is, as a rule, very prompt relief of the feeling of distention and excessive gas formation, a lessening of fatiguability, a lessening or relief of pains in various parts of the body (headache, neuralgic pains in muscles, etc.). The palpitation, tachycardia and nervousness so frequently associated with excessive gas, are also relieved. Patients have commented on the fact that the stools have become less offensive after taking the ricinoleate. Some of our patients who have obtained marked subjective relief have complained of a recurrence of their symptoms when their supply of capsules became temporarily exhausted, with relief soon after resuming the medication. We have attempted to avoid psychic influences by not stating to patients the results we anticipate.

Our experience with this drug is too limited to enable us to state whether it has any effect on the bacterial flora or what its ultimate value may prove to be. We have given as many as six 5-grain capsules daily, though the majority of our patients have received only three daily. The drug appears to be entirely nontoxic in the doses employed; this was to be expected, as it is the sodium soap of castor oil.

Other possible therapeutic applications of this preparation are being investigated in our Clinic and will be reported at a later date.

THE OCCURRENCE OF POSITIVE WASSERMANN REACTIONS IN THE SPINAL FLUID OF TUBERCULOUS AND OTHER NONSYPHILITIC CASES OF MENINGITIS.

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and

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The earliest reference to this subject appears to be that of Zadek,[1] who, in 1918, reported 5 cases of meningitis in which the Wassermann reaction of the blood was negative, while that of the spinal fluid was positive. In 3 of the cases the offending organism was the meningococcus, in one the pneumococcus, and in one the tubercle bacillus. Syphilis was definitely excluded by autopsy as well as by history.

In January, 1927, Zange[2] summarized (in addition to those of Zadek) the reports of Kronfeld, Kraemers, Eicke, Lesser and Stern, each of whom had cited single cases with positive spinal fluid and negative blood in which there was absolute evidence against the occurrence of syphilitic infection. These were cases of epidemic or tuberculous meningitis. Zange further quoted the discussion of the matter by Plaut and Zalociecki who concluded that the results were due to errors of technique. Zange was unable to contradict these opinions, but reported from his own experience a number of cases in which the spinal fluid was negative, though there was evidence of meningeal irritation, clinically and by analysis, while the blood gave positive reactions.

Pilotti[3] presents a case with positive colloidal gold as well as Wassermann reaction in spinal fluid and blood in a former luetic who had had specific treatment, the body of whom at autopsy showed no syphilitic lesions, but those of tuberculous meningitis. He cites similar observations by Hauptmann, Kafka, Assman and Eskuchen, as well as those of Plaut and Zalociecki, of cases of purulent meningitis following otitis media, epidemic meningitis and tuberculous meningitis, Plaut claiming that they were nonluetic meningitides in luetics. Pilotti further cites the reports of tuberculous meningitis and general carcinomatosis by Dungern and Helpern, cerebral neoplasm by Vincent and medullary tumor by Lowenburg, in which there were positive Wassermann reactions of the spinal fluid and negative Wassermann reactions in the blood. Histologically they were nonsyphilitic. He also mentions the presence of a positive reaction in the fluid in tropical sleeping sickness and in leprosy. Another Italian, Podesta[4] adds a case of "Negative Wassermann with positive cerebrospinal fluid findings."

Malcolm, of Vancouver[5] reports 8 atypical Wassermann reactions in a series of 848 spinal fluids, positive with the acetone insoluble antigen of Bordet and negative with the cholesterinized antigen of Kolmer, except in a case of cerebral tumor, which was positive with both antigens. In 3 cases, there were histories of syphilis while the remainder consisted of a case of bulbar paralysis, one of encephalitis lethargica, one of anterior poliomyelitis, one of tuberculous meningitis and the case of cerebral tumor mentioned. The blood reactions were not reported.

As the above reports are so few and scattered, the experience of the Dunn Memorial Clinic seems to warrant publication. Here it has been the custom for many years to make complement-fixation tests of the spinal fluid routinely in all cases of meningitis, in addition to the cell count, estimation of globulin and sugar and microscopic examination. Eight cases are presented from the files of the past five years, all definitely nonsyphilitic, in each of which there was a positive Wassermann reaction in the spinal fluid. The detailed analyses appear in the appended table.

SPINAL FLUIDS OF NONSYPHILITICS WITH STRONGLY POSITIVE WASSERMANN TESTS OF THE SPINAL FLUID.

	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.	Case 7.	Case 8.
Sex	M.	F.	M.	M.	F.	M.	M.	M.
Cells	86	33	..	100	..	400	..	186
Tubercle bacilli	Few	..	+	...	Many	+	..	Few
Lymphocytes	Many small	..	..	Many small	Many small			
Globulin	++	++	..	Slight	+	++++	+++++	++++
Sugar	++	+	..	30 mg. per 100 cc.	++	++	+	+++
Wassermann reaction	++++	++++	++++	++++	++++	++++	++++	++++
Mastic	..	Comp. precip.	..	...	..	..	..	Mening. curve
Gold	..	..	..	...	..	Mening. curve	Mening. curve	
Blood Wassermann	Neg.	Neg.	Neg.	Neg.	Neg.	..	..	Neg.
Clinical diagnosis	Pul. tb.	Pul. tb.	Pul. tb.	...	..	..	Traum. mening.	Pul. tb.

It is noted that in Case 2 there was a complete precipitation by the mastic test. Case 8 showed a meningitis curve by this test, and Cases 6 and 7 by the colloidal-gold test. These additional tests are always made when there is sufficient fluid. Five of the fluids revealed the presence of tubercle bacilli, while Case 7 showed many intracellular diplococci. In the latter, the meningitis was the result of traumatism, in a child who had been struck by a motor-truck. This case and Case 6 were the only ones in which blood Wassermann tests were not made, as they were not seen until the time of the emergency (from the service of Dr. Wm. Pinckney Herbert). Cases 4 and 5 are of particular interest from the fact that Dr. J. LaBruce Ward, who referred them, took the pains to investigate the families and it was found that the blood of the parents and of the other children gave negative reactions, as well as that of the patients. In Case 3, the spinal puncture was made after death and the cells had disintegrated; similar conditions of the cells precluded counts in Cases 5 and 7. In the other cases the specimens were fresh. Cases 1, 2, 3 and 8 were adults who had advanced pulmonary tuberculosis, the others were young children. Case 6 was a negro. In none was there a history of venereal disease.

Naturally, the first question to arise is that of technique. The method which we have employed is that of Kolmer, with the single modification of incubating by means of the water bath instead of the ice box. This procedure has been necessary on account of the large number of patients referred for consultation from a distance, whose time for complete examination is limited, frequently to a one-night "stop-over." The method as modified, had the complete sanction of the late Dr. Dunn, who, early in his career, attained distinction in laboratory research, in which he continued to take an active interest

throughout his extensive clinical experience. In a personal communication, Dr. Kolmer says that he does not think he has ever observed a strongly positive Wassermann reaction in spinal fluids of cases of tuberculous and meningococcus meningitis, in nonsyphilitic individuals by his method, and states that "it is common for such fluid to be anticomplementary and that the controls are apt to hemolyze slowly, but may be completed in the period of secondary incubation and yet show some degree of inhibition of hemolysis in those tubes carrying antigen, due, presumably, to a summation of the effect of antigen alone and spinal fluid alone, upon complement." This opinion is based upon experience with his new method, in which he regards as very important the ice box primary incubation of eighteen hours at 6° to 8° C followed by ten minutes in a water bath at 38° C. It is his belief that the water-bath incubation may be much more likely to give falsely positive reactions. He discusses this matter in detail in his book "Serum Diagnosis by Complement Fixation.[6]" In it he also observes that much less investigation has been devoted to the specificity of complement fixation in spinal fluid than in blood, but that his experience has covered the examination of fluids from all types of nonsyphilitic meningitis (pneumococcus, streptococcus, staphylococcus, meningococcus, tuberculous and influenzal, *with negative reactions in all.* (Italics his.) In textbook "The Cerebrospinal Fluid in Clinical Diagnosis," to our addition to this authority, Greenfield and Carmichael,[8] in their knowledge the most complete work on this subject in the English language, make the flat statement that "The Wassermann reaction is constantly negative with the heated fluid in cases uncomplicated by syphilis."

In rebuttal, it may be said that in one of the cases presented (Case 3) the Kolmer technique was followed throughout without modification. In an exigency, the analysis on the fluid of this patient, who had been under our care, was done in the laboratory of Dr. W. L. Grantham, who, incidentally, informs us that he has observed similar reactions in other cases. Further, if the results were due to an error in technique it would be reasonable to expect their frequent repetition, while the fact is that those submitted are exceptions in a long series of negative results. It is also noteworthy that in the cases under discussion all of the reactions were strongly positive (4+). Moreover, our technique has been thoroughly checked in many ways—first by Dr. Dunn personally, who was never too busy to visit the laboratory one or more times daily, and by means of other laboratories during the early incumbency of the serologist. Parallel tests by means of the colloidal-gold and mastic reactions over a period of years, and with the Meinicke test for several months, to say nothing of the Kahn procedure, have completely corroborated our Wassermann results. These have proved

acceptable to the Chief of the Clinic, Dr. Charles DeWitt Colby, who during the first eight of his seventeen years association with Dr. Dunn, was in charge of the laboratory, to which at that time the city, county and many physicians referred specimens of all kinds.

As for the previous experience of the serologist, it may not be amiss to say that he received his initial training in the Army Medical School in 1910, where at first the original Wassermann technique was used and later that of Colonel Charles F. Craig,[9] under whom he served at Fort Leavenworth, while that officer was becoming an outstanding figure in this field. He commonly performed as many as 100 Wassermann tests per week, and had an abundant experience with spinal fluids in consequence of the Army's policy to withhold discharge from the syphilitic register until the fluid, as well as the blood, was negative. During his connection of seven years with the Dunn Clinic he has averaged about 250 Wassermann tests per month.

If our results are assumed to be free from important technical error, our next consideration should be an explanation of their nature and possible causes. The coincidence of positive spinal fluid and negative blood serum seems to support the idea dwelt upon at considerable length by Pilotti and held by Wassermann, Plaut and Hauptmann, that the antibodies, which are responsible for the Wassermann reaction, are formed in the spinal fluid locally rather than permeating the membranes from the blood stream, as held by Zalociecki, Pilotti and others.

An original suggestion was offered by Dr. D. J. McCarthy, of Philadelphia, to whom an inquiry was addressed, as in addition to being a neuropsychiatrist, he has been associated with the Phipps Institute for many years, and has a rich background as a teacher and past president of the Philadelphia Pathological Society. He refers to "the autopsies at the Phipps Institute, which showed a very marked loss of cerebral substance both as to total weight of the brain and as to the evidence of atrophy of the frontal parietal area, such atrophy corresponding in a general way to the atrophic areas in paresis. The loss of brain substance was also shown in the very widely dilated ventricles." He offers this as a very possible explanation of the presence of the positive Wassermann reaction (presumably due to the increased lecithin and cholesterin) in the spinal fluid.

Another suggestion, which seems quite pertinent, has been advanced by Dr. Alfred Blumberg, pathologist to the Government Hospital at Oteen, to the effect that the reaction may be due to the increase in the number of cells in the fluid, in meningitis, which, by their fatty alcohol content, may change the surface tension sufficiently to cause the reaction.

Our own opinion is that the reaction may be due to the abundance

of microörganisms causing the inflammation, the mere presence of which, alone, may inhibit hemolysis, although it must be admitted that we have had other cases of meningitis with negative findings. In the future, we shall attempt to eliminate this factor by heating a portion of the fluid to the point of inactivation, even though Kolmer[7] believes this to be unnecessary with clear fluids kept at low temperatures and Craig warns against it. We shall also add an estimation of cholesterin to our routine examination, to determine the possible increase of that element from irritation of the meninges, as well as to the increased number of cells.

Finally, we regard the occurrence in these particular cases of the meningitic curve with the mastic and colloidal-gold tests (which is characteristic and quite different from the typical paretic curve), as significant of a process other than syphilis.

Of course, the last word has not been said as to the nature and specificity of the Wassermann reaction, and it is obvious that we have much to learn concerning the spinal fluid. If has long been recognized that it is not a specific complement-deviation test in the strict sense, as is shown by the efficiency of nonsyphilitic substances as antigens. It is curious that so little has appeared so far on the subject here presented, in the English language. It is hoped that more reports will be forthcoming in this country, and that some one may go farther into an explanation of the causative factors.

NOTE.—We desire to thank Dr. W. C. Brownson for the translation of the Italian literature; Dr. J. LaBruce Ward for assistance and inspiration, Dr. Alfred Blumberg for a survey of the German literature and Col. Percy M. Ashburn, of the Surgeon General's Library, for research and suggestions as to the bibliography.

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CLINICAL OBSERVATIONS ON THE USE OF AN OVARIAN HORMONE: AMNIOTIN.

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Clinical studies of supposed hypofunction of the ovaries are seriously handicapped by the lack of an objective and mathematical index of ovarian activity. The situation is analogous to the observations made on hypothyroid syndromes before basal metabolic rates were measured. But both clinical and fundamental scientific profit accrued from the more or less empirical association of certain symptoms with deficiency of thyroid secretion. It must not be forgotten that even technically perfect basal metabolic measurements showing low rates do not in every case demonstrate a hypothyroidism. Clinical observation is just as necessary as before. The status of observations on the menopause, infantilism, amenorrhea and other menstrual irregularities is one of rather empirical grouping based on the history and physical findings. Lacking specific tests for ovarian activity in the human female, the clinician must make diagnoses that are probable rather than certain.

The conviction that the ovary produces a hormone has become a certainty with the demonstration by Allen and Doisy[1] of the active preparations from the Graafian follicle. With this material standardized biologically and shown to be the same in action for a variety of animal species, the clinician has a new means of investigating the disorders supposed to be due to hypoövarian function. It is frankly recognized that clinical results with such a hormone do not prove a syndrome due to lack of the hormone. When, however, the ovaries are known to be losing their activity as at the menopause, the symptoms common to this period may reasonably be supposed to result from a lack of ovarian secretion. If in such cases the administration of a hormone preparation gives definite relief from one or more symptom groups consistently, the probability of the association of cause and effect is greatly strengthened.

Such attempts to establish causative relations must be made with caution. Just as the use of thyroid preparations to hasten the reduction of obesity does not prove obesity always due to hypothyroidism, similar errors may be possible with ovarian hormones.

Furthermore, failure to secure results from use of the Graafian follicle preparations in treatment of symptoms thought to be due to ovarian hypofunction does not prove the diagnosis wrong. It is now recognized that there are at least two hormones obtained from the ovaries of animals. The possible complications are more than doubled by the presence of two hormones, follicular and luteal.

TABLE I.—RESULTS OF TREATMENT WITH AMNIOTIN.

Group.	Type of cases.	No. of cases.	Benefited.	Doubtful.	No relief.
1.	Menopause, with hot flushes and insomnia	15	10	1	4
2.	Headaches with suspected menopause	3	2	..	1
3.	Involutional psychosis	3	..	..	3
4.	Angioneurotic edema, with amenorrhea	2	1	..	1
5.	Infantile female type	2	1	1	
	Totals	25	14	2	9

With these possibilities in mind, we present a study of 25 cases that have been treated with amniotin. This is a preparation of the Allen and Doisy hormone secured from amniotic liquor of cattle. It is an aqueous solution, prepared for subcutaneous injection, in a concentration of 10 rat units per cubic centimeter. This material was supplied to us by the laboratory of E. R. Squibb & Sons. The standardization has been checked for us in the laboratory of Dr. F. L. Hisaw of this University. In several of these cases where subcutaneous injections had been followed by therapeutic relief we tried the use of vaginal pessaries of amniotin. These were prepared in glycerinated gelatin, containing 10 units per gram. They were furnished likewise by the Squibb laboratory.

The diagnostic grouping of our cases is indicated in the table of results. In Group 1 we have placed those women who had ceased menstruating or who were reporting the irregularity of menses which often precedes the menopause. In these cases the "hot flashes" in the skin of the face and neck, insomnia, variable increase in blood pressure, and frequent headaches are common symptoms. Obesity occurs frequently. Group 2 is different in that hot flashes were not reported. A menopause was suspected because of menstrual changes, accompanying or preceding the headaches. Group 3 represents an association of a known menopause within the few years preceding the gradual development of mental depression, melancholia, a sense of general inadequacy, and idea of reference. The menopause is assumed by some clinicians to be at least a factor in causing this psychosis. Group 4 is merely an empirical association of angioneurotic edema with ovarian disturbance because amenorrhea or the menopause occurred at about the time the attacks of edema first appeared. In Group 5 we attempt to include

only those female infantile cases in which there is no apparent involvement of the thyroid or pituitary glands.

We have made no attempt here to carry out systematic comparisions of the results from this treatment with those secured in our experience by the use of the other preparations of the ovary and corpus luteum. We have, of course, seen cases that were benefited by those other preparations. We have studiously omitted medication with depressants such as bromids or barbital and its analogues. Recognizing the frequency with which the vasomotor phenomena of the menopause may spontaneously and suddenly subside, we were prepared to see some results with any preparation tried. We feel, however, that the way in which immediate relief from hot flashes has followed on the days when amniotin was given, to return equally promptly when it was omitted, makes spontaneous improvement in so many cases entirely improbable.

A few case summaries follow. Successful issue of the treatment need not be described in detail except where particular features may be of interest in showing the unusual factors in the clinical course. The failures are mentioned in sufficient detail to show that failure might have been predicted.

Group 1. CASE I.—Mrs. D., aged fifty-eight years, complained of nervousness, insomnia, hot flashes eight to ten times daily, and pelvic pain. Physical examination showed nothing unusual. Some menopausal symptoms had been present for eight years. The use of 10 units of amniotin daily gave immediate relief. On the evening of the second day, six hours after the injection, there was an unusually severe flash, accompanied by peculiar abdominal symptoms and urinary urgency for six hours. Reduction of the dose to 5 units daily was followed by the return of an occasional flash. Insomnia was relieved at once. Transfer to the use of pessaries containing about 8 units each, inserted on alternate nights, again gave complete relief. Use of the pessaries on every third night was not quite adequate to prevent hot flashes. After several weeks, relief from hot flashes required the use of 10-unit pessaries daily, and still later the return to the use of 15 to 30 units hypodermically. Ten units hypodermically were no more effective at this time than when given by vaginal route.

CASE II.—Mrs. N., aged forty-three years, complained of obesity, insomnia, and hot flashes. Menses had continued after unilateral ovariectomy in 1925. First evidence of menopausal symptoms appeared in 1926. Hot flashes were irregular in occurrence, but few days passed without them. Ovarian tablets had given partial relief. Use of 10-unit doses of amniotin daily gave complete relief from the flashes and insomnia. Transfer to the use of 10-unit pessaries was made after only a few days because of pain from the use of the hypodermic (not after, but during the injection). Relief was not as complete until the pessary was retained by the use of wool tampons inserted into the vagina and allowed to remain overnight.

CASE III.—Mrs. O., aged thirty-one years, was convalescent from cholecystectomy and complained of irregular and profuse menstruation with very frequent hot flashes, for about one year. There was a marked hysterical history. Use of 10 units of amniotin daily gave marked relief from flashes

and general improvement in the sense of well being. An interval of forty-eight hours without treatment was followed by flashes eight to nine times daily. A 50-unit pessary was then used. She experienced an extreme chill, sweat and discomfort for over twenty-four hours, but was free from flashes for about forty-eight hours. Trials of smaller doses showed that, except for times of unusual nervous excitement the use of 12.5-unit pessaries was required about once in forty-eight hours to completely prevent hot flashes.

CASE IV.—Mrs. W., aged twenty-eight years, was admitted for treatment of diabetes mellitus. She was also severely anemic, as the result of bleeding hemorrhoids, had acute colitis and a history of bilateral ovariectomy and salpingectomy for gonorrheal infection. The rather peculiar subjective hot and cold feelings were at first thought to be due to insulin reactions, but this was conclusively disproved. Follicular hormone was used, 10 units daily for nine days, with some improvement. Lutein by mouth after that continued to give some relief. This case is recorded as doubtful.

Four patients who received no relief included an obese woman with cholecystitis, who left the hospital on the third day of the trial; a woman who had only objective manifestations of the flashes, and kept no record of the result of treatment since there was no subjective improvement in her long-standing spastic colitis which was her chief complaint at the time; and a woman whose menses were beginning to change in type, but who was considered to be essentially thyrotoxic. In the fourth case, hot flashes were only one of many complaints for which surgical intervention had been tried repeatedly, but in vain.

It is apparent that in 10 of the 15 cases found in this group results were satisfactory. These patients have been glad to continue the treatment. In the other 5 cases, success was hardly to be expected in at least 4. Success in two-thirds of these cases really understates the facts.

Group 2. Among the 3 cases of headache probably associated with the menopause, the success was not so definite as with the hot flashes. Two were, however, well pleased.

CASE V.—Miss G., aged forty years, was a severe asthmatic, with pulmonic artery enlargement and a retrosternal thyroid. Headaches occurred daily during periods of amenorrhea, which has been frequent for six years. Lutein hypodermically gave partial relief, but this relief was definitely greater with the use of 10 units daily of amniotin. Similar relief was procured during a second period of amenorrhea. Headaches never occur when menses are regular.

CASE VI.—Miss B., aged thirty-eight years, found similarly more uniform relief from headaches and asthenia with amniotin than with lutein.

CASE VII.—Mrs. L., aged thirty-four years, had numerous complaints, and was considered hysterical. Hysterectomy had been done fourteen years before. Headaches were particularly disconcerting. Use of 10 units of amniotin daily for five days, then 10 units twice daily for four days, gave no relief. The basal metabolic rate was from 13 to 23 per cent below the Du Bois normal prediction. The use of thyroid medication to elevate the

rate gave slight improvement. Successful issue to the amniotin therapy could hardly be expected.

Group 3. The three cases of involutional psychosis studied have shown no benefit. One had 10 units daily for five days, the others had similar doses for periods up to three weeks. In one case there was possibly temporary improvement. This field may require more prolonged use of the amniotin, or probably a different type of substitution therapy.

Group 4. One of the two cases of angioneurotic edema observed was found to be complicated by a low basal metabolic rate. There was no improvement in the edema or the amenorrhea, of seven years' duration, by the use of amniotin.

CASE VIII.—Mrs. F., aged twenty-eight years, had a partial hysterectomy and ovariectomy in May, 1927. Angioneurotic edema appeared a year later. The attacks seem to be worse in periods of about one month. Treatment before we saw this patient had included soda, mineral oil, dietary restrictions, calcium salts, thyroid, nasal treatment, ovarian tablets, bromids, belladonna and morphin, as well as epinephrin in attacks. None of these had given any real relief. Over a period of three months with varying doses of amniotin it has been apparent that the edema attacks are greatly limited in frequency and intensity by doses of 10 units daily. The use of the 10-unit pessaries of amniotin is of service. The melting of the gelatin led to sufficient vaginal drainage and loss of material, even at night, so that the use of wool tampons was found necessary. This improved the results. After a few weeks this patient reported personality changes which are usually interpreted as a return of more normal secondary sex characteristics.

Group 5. The treatment of 2 cases of amenorrhea with incomplete development of female characters presents a most interesting test of the hormone value of amniotin. Only 2 such young women have been treated in the course of the eight months' use of amniotin. One of these shows questionable benefit from the treatment; the other very gratifying and positive development.

CASE IX.—Miss G., aged twenty-eight years, had been observed during three different periods of hospitalization, with such tentative diagnoses as hyperthyroidism, neurocirculatory asthenia, and polyglandular dyscrasia. In October, 1928, it was observed that the hair distribution was masculine in type, although concealed by shaving, the breasts were undeveloped, the hymen almost imperforate, the external genitalia infantile. Menses had begun at fourteen years of age, but had been irregular, with scanty flow. The interval had become about three months. The basal metabolic rate, which had been +5 and +17 per cent (Du Bois standard) on previous observations, was now 15 per cent below the same standard. Ten units of amniotin were given daily, beginning October 25. After five weeks there was a report of definite increase in appetite and weight. The hymen was incised at this time. Pelvic examination showed the internal genitalia to be of normal development. Two weeks later the patient reported that she was making subjective improvement. She had just experienced sensations in her right side which usually had been prodromal of menstruation. No flow had been seen for five months. The basal rate was now 11 per cent

below the standard. Amniotin was given in 12.5-unit pessaries daily for two weeks.

On December 28, after nine weeks of amniotin therapy, she reported consistent gain in weight and sense of well being. Amniotin was stopped, unfortunately, and thyroid given daily, in 1-grain doses. Two weeks later the basal rate had come up to the standard, the patient said she felt better than for many months, and menstruation appeared in more profuse flow than usual for her. Unfortunately for the experiment, it is not possible to evaluate either the thyroid or follicular hormone part of this therapy. The patient later reported that she was not feeling as well after two more weeks on thyroid alone. The thyroid was stopped, shortly before the expected next menstrual flow, but no menstruation occurred. Resumption of the use of amniotin was followed by the appearance of a delayed flow about five weeks later. We are tempted to attribute much of the progress to the amniotin, although the case must be recorded as doubtful at best.

Case X.—Miss S., aged twenty-three years, was admitted to the neurological service for what proved to be a hysterical fracture of the left elbow. She had several hysterical episodes in her history. No menstrual flow had ever been seen. Breasts and genitalia were infantile. Amniotin was given in doses of 10 units daily for several weeks. After return to her home the patient continued the use of the injections, but was at times irregular. For a time the dose was 5 units twice daily, then 5 units daily and then was omitted for ten days out of each month. The first symptom reported was tingling in both breasts. This was present from the first week of the treatment and persists. By the end of a month there was notable increase in hair growth in the axillæ and at the pubic line, and the mammæ were developing. On readmission to the hospital after ten weeks' treatment there was a gain of 15 pounds, further hair and mammary growth, and the patient had developed a peculiar shy attitude toward male members of the staff—apparently an exaggerated sex consciousness. Her conversation showed that she was experiencing personality changes similar to those of an adolescent girl.

Beginning five months after the treatment started and recurring at four-week intervals the next two months she reported a slight papular rash followed after three days by nausea, and then after three to four days by cramplike pelvic pain. At the time of the third recurrence she was again in the hospital and the pelvic pain was followed by dark yellow vaginal flow, the first she had ever experienced. The nausea, pelvic pain and pelvic tenderness continued for over a week, manifestly being hysterically exaggerated. The same gynecologist who had made previous examinations reported a development of genitalia and of mammary tissue and hair which was quite surprising.

Although the subjective manifestations must be somewhat discounted because of the hysterical tendency here, the objective development and the personality change have given ample evidence that the amniotin has accomplished real feminization in this patient.

Discussion. It appears to us from this series of cases that amniotin possesses the activity for the human female which the animal experiments of Allen and Doisy would lead us to predict. In the hot flashes, insomnia, nervous instability, and headaches attributable to the menopause, artificial or spontaneous, amniotin has given very satisfactory relief. The improvement in angioneurotic edema associated with partial menopause confirms this point of view.

Most convincing of all is the development of an infantile type under the administration of the preparation.

The manufacturers of this preparation, as well as others, have recommended the use of much larger doses than we have employed. For the menopausal symptoms, we feel that doses of about 10 units daily are adequate, and may occasionally be excessive. A dose of 50 units was definitely too large.

The activity of amniotin in the form of vaginal pessaries was demonstrated on spayed monkeys in the laboratories of E. R. Squibb & Sons. We are convinced that the same result may be obtained in women. There are two difficulties to be encountered. One is that unmarried women are apt to object to this method. The other is that except with very firm closure of the vaginal sphincter there is sufficient drainage after the melting of the gelatin to occasion discomfort and loss of material. This is preventable by the use of wool or cotton vaginal tampons. Absorption from vaginal mucosa evidently goes on rapidly enough to allow of the use of a pessary retained overnight.

The occasion for the use of pessaries is the avoidance of the need of a hypodermic. Pessaries were used successfully in 7 of these cases. There has been no pain incident to the injection of amniotin in liquid form other than that occasioned by any hypodermic medication. Neither have we seen any evidence of serum reactions or hypersensitization phenomena.

Evaluation of this new material in comparison with the many older ovarian preparations is difficult at present. In contrast to the usual expectation based on experience with ovarian material by mouth, amniotin shows its activity at once in the cases of hot flash, insomnia, and nervous instability. It requires use at intervals of not over seventy-two hours, excepting in one case observed near the end of menopausal difficulty. This is to be correlated with the presence of the hormone in urine, indicating its rapid excretion. Since some of our patients have experienced relief from the use of lutein, we are inclined to believe that the commercial preparations of luteal material have been active largely because of their content of the follicular material. This is confirmed by the recent work of Hisaw.[2]

Summary. The effect of amniotin, an ovarian hormone secured from the amniotic liquor of cattle, has been studied on 25 women with menopausal and menstrual disturbances. Its use has been of marked value in the relief of the vasomotor phenomena of the menopause, and in promoting feminine development of one woman of infantile type.

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THE CURATIVE AND POSSIBLY SPECIFIC EFFECT UPON COLDS OF VACCINES CONSISTING OF THE STREPTOCOCCI PREVALENT DURING THAT PERIOD.*

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In a recent paper[1] evidence was presented that vaccines, consisting of the more prevalent types of streptococci during a certain period, prevented colds during that period to a considerable degree. The present paper concerns more especially the relief or cure of acute colds by vaccines consisting of the varieties of streptococci that were most prevalent during the periods when the colds occurred, and in many instances a specificity among the streptococci, that seemed to cure, is demonstrated.

In this paper are presented as many of those patients, as it was possible to study, who were presented and mentioned in the former paper[1] and had had incomplete relief from colds following the preventive treatment. Since the patients presented themselves as soon as they were sure that they had a cold and not later than forty-eight hours after the onset of the symptoms, it was possible to use a vaccine for its curative effect. The result and type of vaccine used seemed to offer an explanation why the preventive inoculations had not been entirely successful and to demonstrate in some instances a selectivity or specificity among the streptococci in addition to the curative effect. Another group of patients who were repeatedly treated for acute colds are presented to show the curative value and in some instances a selectivity or specificity of the streptococcus group. The majority of these patients had not been given the preventive inoculations but were treated only when they had a cold. Some, however, had had preventive innoculations but many months had elapsed between the preventive inoculations and the next cold, and a few patients had had incomplete relief from the preventive inoculations.

In Table I will be considered 19 of the 97 patients who were presented in the tables of the former paper;[1] these 19 patients will be reproduced from the former paper. The first 10 patients were in Table II, the next 3 were in Table III and the last 6 patients were in Table IV. In Table II will be considered 20 of the 87 patients who were mentioned in the discussions of the tables in the former paper[1] but were not included in the tables because some received irregular and infrequent treatment, and others were given an autogenous

* All of the patients were treated in private practice. The laboratory work was done with June Adkinson in the Medical Laboratory of the Peter Bent Brigham Hospital, Boston, Mass.

vaccine at times. In Table III are presented 15 patients who were repeatedly treated for acute colds.

As a rule, the patient presenting himself for treatment for an acute cold was given an initial dose, which was 3 minims, or 0.2 cc., of the mixed streptococcus vaccine, which comprised the more prevalent varieties of streptococci at that time and which were being used as a preventive at that time. Some patients, who had been given the preventive vaccine from which one of the most prevalent varieties of streptococci had been left out, either purposely or unknowingly at the time, were given a vaccine of only the one variety of streptococcus which was omitted in the preventive course of treatment and which was prevalent enough to have been given and ought to have been included in the mixed preventive vaccine. This experiment was tried with a few cases in 1925 with the Streptococcus subacidus, in 1926 with the Streptococcus hemolyticus Type I and in 1927 with Streptococcus salivarius. Of the patients with whom this was done all had had a cold from two to six weeks after the completion of the preventive vaccine from which the particular variety of streptococcus was omitted, so that it was possible to assume that that particular variety of prevalent streptococcus was probably the cause of the cold and since usually prompt relief followed the use of it as a vaccine this would seem to show specificity among the varieties of streptococci as to the cause and cure of some colds.

For the relief or cure of acute colds the vaccine offers the best and most prompt result, as a rule, if given between twenty-four and forty-eight hours after the onset of a definite cold. When the vaccine is given during the first few hours after the onset of symptoms of a cold, often the patient will state that the cold was aborted and occasionally he will state that it was made worse. Naturally, neither observation may be correct because there is no way of determining whether there would have been a cold at all in the former and no way of telling the severity in the latter case. Since for a short period following a dose of vaccine the resistance of the individual is supposed to be temporarily lowered and since the resistance is naturally already lowered at the onset of a cold, these are sufficient reasons to delay the use of the vaccine until the second twenty-four hours of cold symptoms and then the resultant effect of the vaccine is more evident. Most of the patients in this paper were treated between twenty and thirty-six hours after the onset of cold symptoms. Many experienced prompt relief, that is, they were either relieved or greatly improved on the day following the dose of vaccine. If they were only improved on the first day following the use of the vaccine, they had to be either relieved or practically free from the cold symptoms on the second or third day at the latest in order to be considered as prompt relief. In other words, there must be at least marked benefit during the first day

following the use of the vaccine and the benefit must rapidly increase during the succeeding two days so that the patient is well within three days after the treatment.

If, during the preventive course of inoculations, a patient has a cold at the time for the next succeeding dose of vaccine, the dose of the preventive vaccine should not be increased but instead the previous dose should be repeated and at the next regular visit the dose may be increased according to the regular schedule. An increase of the dose of the vaccine over the previous dose when the patient has an acute cold is usually followed by more severe symptoms; the explanation already given in the previous paragraph probably holds true. If, however, during the preventive course of treatment the patient develops a cold between inoculations but the acuteness of the cold has markedly subsided, the usual increase in the dose of the vaccine may be given. For further information concerning the administration of the preventive vaccine the previous paper[1] may be consulted.

The previous paper[1] details the composition of the mixed streptococcus vaccine which was used in this paper during the various years and the method of its administration. Before considering the first two tables, however, it might be well to explain the various symbols. The first column carries a number which represents a patient; in the second column the capital letter C means that the patient was under twelve years of age, and a blank means an adult; in the third column a capital letter C means that the patient was subject only to colds, a capital letter A means that the patient had asthma associated only with colds. The remainder of each table consists of groups of three columns; in the first column of each group is noted the year in which treatment was given, in the second column the result and in the third column the period of time in months between courses of vaccine. In the second or result column of each group certain symbols need to be explained. The capital letter W means that the patient considered himself well so far as colds or colds and asthma were concerned, the letter N means that the patient was well until "now" or very recently prior to the next course of vaccine or was well for the number of months indicated in the preceeding column. The symbols 1c mean that the patient had one cold during that interval and 1a means one attack of asthma. The letters SC mean slight colds which were of slight consequence and in an asthmatic patient the colds did not cause asthma. The capital letters PF mean that the patient considered himself practically free from colds or asthma; although he may have had slight colds or asthma, yet in comparison to the years previous to treatment he considered himself to be very well.

In Table I, as already stated, are presented 19 patients that are reproduced from the preceding paper.[1] From Table II of the preceding paper,[1] there are ten patients who were designated by the

following numbers, 1, 3, 4, 6, 12, 17, 18, 24, 28 and 34. From Table III, 3 patients, Nos. 9, 18 and 19, and from Table IV, 6 patients, Nos. 5, 8, 10, 19, 21 and 24, are reproduced. All of these patients had had preventive treatment and were treated also at the time they had a cold and the result of treatment will tend to show that the vaccine had curative value and in some instances there seems to be demonstrated a specificity among the streptococci.

TABLE I.

No.	Old No.	C = child.	C = cold, A = asthma.	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†
1	Table 2 Pt. 1	C	C	21	1c	6	22	1c	12	24	3c	18	25	1c	12	26	1c	12	27	1R	TR
2	" 2 " 3	...	C	21	W	22	23	W	24	25	1c	13	26	W	12	27	1c	12			
3	" 2 " 4	...	A	21	N	4	21	N	5	22	2c	18	23	N	14	25	N	23	26	W	18
4	" 2 " 6	C	C	22	2c	16	23	W	14	25	W	11	26	W	12	27	W	18			
5	" 2 " 12	C	A	23	W	12	24	W	13	25	N	16	27	1c	12						
6	" 2 " 17	...	A	23	N	6	24	N	10	24	2c	24	26	1c	18						
7	" 2 " 18	...	A	23	W	6	24	1c	12	25	W	12	26	1c	18						
8	" 2 " 24	...	C	23	1c	12	24	W	12	25	W	12	P	F	si	nc	e				
9	" 2 " 28	C	C	23	N	16	25	W	7	25	1c	30									
10	" 2 " 34	...	A	20	3c	24	22	N	60												
11	" 3 " 9	...	A	24	W	12	25	..	..	26	1c	12	27	1c	12						
12	" 3 " 18	C	C	24	PF	12	25	W	12	26	W	12	27								
13	" 3 " 19	C	C	24	W	12	25	W	12	26	PF	12	27								
14	" 4 " 5	C	A	25	N	9	26	N	9	27	1c	12									
15	" 4 " 8	...	C	25	W	9	26	W	13	27	W	12									
16	" 4 " 10	C	A	25	1c	12	26	N	14	27	1c	12									
17	" 4 " 19	C	A	25	1c	12	26	1c	12	27	1c	12									
18	" 4 " 21	...	C	25	W	12	26	W	12	27	1c	12									
19	" 4 " 24	C	C	25	2c	12	26	N	15	27	W	12									

* 1c = one cold; W = well; N = well until now; PF = practically free.
† Months between courses of vaccines.

Case Reports. CASE 1.—The patient, a boy, was subject to frequently repeated colds which were associated with redness of the throat, catarrhal condition of the Eustachian tubes, and discharging ears and fever. After the first course of vaccine (in 1921) he had one cold which appeared four months after his previous preventive inoculation, he was given an initial dose of the mixed vaccine and the cold was relieved in two days without his other usual symptoms. After his second preventive course of vaccine (in 1922) he had one cold which appeared six months after treatment, since it was a severe cold, rather than to give the usual vaccine, an autogenous vaccine was used following which the cold rapidly subsided. After the third course of vaccine (in 1924) he had three colds, the first one came eleven months after the preventive course of vaccine and was so mild that no treatment was given, the second cold appeared four months later still and was relieved in two days after an initial dose of the mixed vaccine, the third cold appeared three months later still and like the former one was promptly relieved. Following the course of preventive vaccine in 1925, he had a cold eight days after the last dose. Since during the preceding

two months the hemolytic subacidus type of streptococcus was very prevalent, but was not present in the vaccine which the patient had been receiving, an initial dose of vaccine of this organism was given, following which the cold disappeared in two days and the patient was free from colds for the succeeding twelve months. After the 1926 course of vaccine, the patient had a cold inside of three weeks, at this time the hemolyticus Type I was prevalent and as it was not included in the preventive vaccine, an initial dose of it was given and the cold symptoms were rapidly relieved and he was free from colds for the remaining twelve months. In 1927 no preventive course of vaccine was given because the patient had been so free from colds during the previous two years. During this twelve-month period the patient had three colds. One of the colds was not relieved by an initial dose of the mixed vaccine and it disappeared only after two doses of an autogenous vaccine. Three weeks later another cold appeared and it was relieved in two days by an initial dose of the mixed vaccine.

This case illustrates many different points which this paper will attempt to bring out. Previous to preventive vaccine treatment and the year that the preventive treatment was omitted, the patient had several colds, some of which were quite severe, however, during each of three-year periods (1922, 1925 and 1926) that the preventive treatment was given the patient had only one cold and that not severe. The one cold that the patient had in 1921 and two of the colds he had in 1924 were relieved in two days by an initial dose of the mixed vaccine. Following the course of vaccine in 1924, the patient had three colds in eighteen months, the first one appeared eleven months after the preventive treatment and was too slight to require treatment, the next one appeared four months later still or fifteen months after the preventive treatment, therefore the result from preventive treatment was successful for over a year.

In 1925 and 1926 the patient had a cold eight and sixteen days, respectively, after the last dose of preventive vaccine. Since many other patients had not had a cold following a course of the mixed vaccine and since this patient the previous year was free for eleven months, the logical assumption was that a bacterium other than those with which he had been treated was the cause of the cold. In 1925 the Streptococcus hemolyticus subacidus was prevalent at the time the patient had the cold, but it was not present in the preventive vaccine, therefore, the patient was given an initial dose of a vaccine consisting only of the subacidus variety and the cold subsided in two days. In 1926 the same reasoning was applied and the same procedure was followed with the exception that Streptococcus hemolyticus Type I was the particular organism involved, and prompt relief followed its use as a vaccine. Each of these two instances would seem to indicate specificity among the streptococci and lack of group polyvalent or nonspecific protection.

Case 2 (Pt. No. 3).—Patient had a cold two months after the preventive course of vaccine was given in 1925, as did the previous case. Also, as in the previous case, since the preventive vaccine did not include hemolyticus subacidus and at the same time it was prevalent, this patient was given an initial dose of subacidus vaccine, following which cold was relieved on the second day. In 1927 this patient had a cold five weeks after the completion of the preventive course of vaccine which had contained all of the most prevalent types of streptococci, therefore, an initial dose of the mixed vaccine was given and the cold was relieved on the second day. Therefore, this patient would seem to illustrate in two instances the curability of streptococcus vaccine in acute colds and in the first instance there is more evidence in favor of specificity than of nonspecificity among the varieties of streptococci in the treatment of colds.

CASE 3 (Pt. No. 4).—The patient, following the preventive vaccine in 1922, had two colds, the first appeared nine months after the course of vaccine and it was rapidly relieved without asthmatic symptoms following an initial dose of the mixed vaccine. The second cold appeared eight months after the first cold or seventeen months after the preventive course of vaccine, and it was not benefited until after two doses of the mixed vaccine had been given with an interval of a week between them.

CASE 4 (Pt. No. 6).—A boy, aged nine years, who had had frequent colds in winter since the age of six years, two years previous to treatment had sinus infections with the colds, and in the spring previous to treatment he had a severe cold with myocarditis, two years previous to treatment his tonsils and adenoids had been removed. Following the preventive vaccine treatment in 1922 the patient had two colds, one which occurred ten months after the completion of the treatment lasted five days, but was not sufficiently severe for treatment, the other cold appeared thirteen months after the preventive treatment and it subsided on the second day after an initial dose of the mixed vaccine.

CASE 5 (Pt. No. 12).—A boy, aged five years, was subject to colds which were accompanied by asthmatic attacks. Following the preventive treatment in 1925 he was well for sixteen months, at the end of which time he began to have asthma, several increasing doses of the mixed vaccine resulted in no benefit. An autogenous sputum vaccine was prepared containing a pure culture of Staphylococcus pyogenes aureus, each treatment with this vaccine was followed by increasing benefit until there was relief after the third dose and the vaccine was stopped. The lack of benefit from the use of the mixed streptococcus vaccine and the rapidly progressive benefit during treatment with the Staphylococcus pyogenes aureus vaccine would indicate specificity among the bacteria in this case. In 1927, five months after a course of the preventive vaccine, the patient had a return of asthma and again an autogenous Staphylococcus pyogenes aureus vaccine relieved the condition.

CASE 6 (Pt. No. 17).—A man, aged fifty-four years, had been subject to head colds for ten years and to attacks of asthma which became so frequent that he was rarely free from it for more than two weeks, with the exception of the summer months. During the two-year period following the preventive vaccine in 1924, the patient had two colds, one appearing eight months and the other nineteen months after the preventive vaccine, in both instances following an initial dose of the mixed vaccine there was prompt relief from the cold in two days and no asthma developed. Following the preventive vaccine in 1926, the patient had two head colds, each of one day's duration, and sixteen months later he had a cold of several day's duration, from which he recovered two days after an initial dose of the mixed vaccine.

CASE 7 (Pt. No. 18).—A man, aged sixty-four years, had been subject to asthma chiefly with colds for the last three years with the exception of the summer months. In 1924, five months after the preventive vaccine treatment, the patient had more or less asthma which gradually disappeared while he was being given three doses of the mixed vaccine. In 1926, nine months after the preventive treatment, the patient had a cold and asthma, both of which rapidly improved following an initial dose of the vaccine.

CASE 8 (Pt. No. 24).—A middle-aged man, who was susceptible to colds, had a severe cold six months after the preventive treatment in 1923. The cold was not benefited by an initial dose of the mixed vaccine, but it rapidly

improved following an initial dose of an autogenous sputum vaccine which consisted of Streptococcus nonhemolyticus fecalis. Since an initial dose of the autogenous vaccine contained six times the quantity of fecalis that was present in an initial dose of the mixed vaccine, it is probable that the benefit which resulted was due to the larger amount of the causative bacterium, fecalis. Since the total quantity of bacteria was the same in both inititals doses this would rule out nonspecificity at least and would tend to show specificity among the streptococcus varieties.

CASE 9 (Pt. No. 28).—A boy, aged eleven years, had been subject to frequent colds and bronchitis for two years with the exception of the summer period. Twenty months after his preventive course of treatment in 1925 he had a cold which was relieved on the day following an initial dose of the mixed vaccine.

CASE 10 (Pt. No. 34).—A middle-aged woman, a school teacher, had averaged five or more colds with asthmatic attacks for each of the last three years. During the two years following the preventive course of vaccine in 1920 she had three colds, four months, twelve months and sixteen months, respectively, after the course of vaccine was completed. In each of these three instances the cold was cured in two days without any asthma following an initial dose of the mixed vaccine.

CASE 11 (Pt. No. 9, Table III).—In 1925 the patient was given no preventive course of vaccine. During the twelve-month period he had five colds at irregular intervals and in each instance after an initial dose of the mixed vaccine the cold was relieved by the second day without asthma, which formerly was associated with colds. Two months after the preventive vaccine in 1926 the patient had a cold, and since the hemolytic Type I streptococcus was prevalent at this time and was not included in the preventive vaccine, he was given an initial dose of a vaccine consisting of this type of streptococcus, following which the cold was promptly relieved. Following the preventive vaccine in 1927 the patient had a cold which subsided in two days after an initial dose of the mixed vaccine.

CASES 12 and 13 (Pts. Nos. 18 and 19).—The patients, who are brothers whose ages in 1927 were eight and ten years respectively, had been given the preventive treatment three successive years with successful results, but in 1927 the preventive treatment was not given. During the succeeding twelve months each patient had three colds, with the former patient they were confined to the head and with the latter they were in the head and chest. In each instance rapid improvement to prompt relief within two to three days followed an initial dose of the mixed vaccine.

CASE 14 (Pt. No. 5).—A boy, aged four years, who had been very susceptible to colds followed by bronchitis for three years and during the last year had also had asthma. In 1925 and 1926 he was free from colds, bronchitis and asthma for nine months following the usual preventive course of vaccine. In 1927 he was given only five of the customary eight or nine preventive treatments and five weeks later he had a cold and asthma for two weeks before he was given treatment. The initial dose of the mixed vaccine was followed by improvement and a second dose a week later was followed by relief.

CASE 15 (Pt. No. 8).—A middle-aged woman who had for years been very susceptible to head colds accompanied by hoarseness and irritation of the throat. Following the completion of the preventive treatment in 1925,

1926 and 1927, she was free from colds, however, during the course of the treatment in 1927, after she had received seven doses of the vaccine, she did have a cold. It is to call attention to and emphasize this that the case is mentioned. Not infrequently do patients during the first two or three weeks of treatment have a cold, probably because sufficient resistance has not yet been developed. After six, seven or more doses of vaccine have been given, the patient sometimes has a cold, this may be due to lack of development of sufficient resistance or to temporarily diminished resistance which probably occurs during the twenty-four-hour period following the larger doses of vaccine. In the particular case at point the patient's sputum contained five varieties of streptococcus and four of these were present in the preventive vaccine, the other being an unusual one. This would seem to indicate that the preventive vaccine was not at fault. When the patient has a cold at the time a treatment is due, the dose of vaccine should not be increased, but instead the preceding dose should be repeated.

CASE 16 (Pt. No. 10).—A boy, aged twelve years, had had frequent attacks of asthma for several years and had always been very susceptible to head colds, he would be free from colds or asthma for only a few weeks at a time. Following the preventive vaccine in 1926 and 1927, he had a cold eight and six months, respectively, after completion of the vaccine treatment. In both instances an initial dose of the mixed vaccine was followed in two days by relief of the cold without any asthma.

CASE 17 (Pt. No. 19).—A boy, aged three and a half years, had since birth been very susceptible to head colds and during the last year he had had four attacks of asthma with colds, his adenoids had been removed at the age of two years without benefit. In 1925, two weeks after completion of the preventive vaccine he had a head cold from which he recovered in two days following an initial dose of the mixed vaccine. In 1926 he had a cold and asthmatic attack six months after the preventive vaccine, and he was not relieved until a second dose of the mixed vaccine was given. In 1927 he had one cold of two days' duration with very slight asthma.

CASE 18 (Pt. No. 21).—An adult male, had had frequent colds ever since he could remember. In 1927 six months after the preventive vaccine, he had a cold accompanied by aches and pains, sore throat, and general malaise which was called "grippe" by his local physician. After he had been ill for two days with these symptoms he was given an initial dose of the mixed vaccine which was followed two days later by relief.

CASE 19 (Pt. No. 24).—A boy, aged six years, had been subject to a head cold every three weeks with the exception of the summer period for several years. Following the preventive treatment in 1925 he had two head colds, one appearing two months and the other three months after the preventive treatment. The first cold was relieved on the day following an initial dose of Streptococcus hemolyticus subacidus which was given for reasons already mentioned in two previous instances and the second cold was relieved on the second day after an initial dose of the mixed vaccine.

In Table II are reported 14 of the 87 cases that were referred to in the previous paper[1] in the discussion of the tables but were not a part of the tables and, in addition, 6 other patients; namely, No. 4 and the last 5 in this table, that have not previously been mentioned.

TABLE II.

Number.	C = child. C = cold. A = asthma.	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†	Year.	Result.*	Months.†
Patient 1 . .	... A	21	3c	23	23	1c	10	24	2c	13	25	3c	24	27	2c	12			
" 2 . .	... C	22	5c	36	25	2c	12	26	1c	12	27	W	12						
" 3 . .	... A	22	N	12	23	N	16	25	N	12	26	1c	12	27	W	12			
" 4 . .	... A	23	...	...	24	...	...	25	sc	14	26	N	9	27					
" 5 . .	... A	20	N	9	21	N	9	22	...	...	27	W	12						
" 6 . .	... A	24	N	8	24	N	11	25	N	14	26	N	10	27	N	13			
" 7 . .	... C	25	1c	12	26	2c	12	27	1c	12									
" 8 . .	... A	24	N	33	26	2c	12	27	2c	12									
" 9 . .	... A	22	...	...	23	N	28	25	W	30									
" 10 . .	... A	23	...	...	24	PF	30	27	1c	12									
" 11 . .	... A	20	N	22	22	N	24	24	N	24	26	N	21						
" 12 . .	... A	23	1a	20	25	PF	20												
" 13 . .	... C	25	2c	18	26	2c	24												
" 14 . .	C A	24	1c	13	26	W	12	27	no	tr.									
" 15 . .	... A	20	1c	12	21	1c	12												
" 16 . .	C A	25	...	...	26	W	18												
" 17 . .	C A	25	2c	36															
" 18 . .	C C	25	1c	24															
" 19 . .	C C	25	2c	24															
" 20 . .	... C	22	W	8															

† 1c = one cold; W = well; N = well until now; PF = practically free.
* Months between courses of vaccines.

Case Reports, Table II. Patient No. 1 is a female aged fifty years, a school teacher who for fifteen years had been subject to frequent colds and bronchitis with some asthmatic attacks. When first seen in 1920, since she was having an attack of bronchitis and asthma, an autogenous sputum vaccine was given and after three treatments she became free from symptoms. In 1921 the preventive vaccine was given, following which she had three colds in the succeeding twenty-three months. The first cold appeared fourteen months after the preventive treatment and it was relieved three days after an initial dose of the mixed vaccine, with no bronchitis or asthma. The second cold appeared twenty months after the preventive treatment, and, like the former, subsided without other symptoms after an initial dose of the vaccine. After the third cold, which came three weeks later, another course of the preventive vaccine was given, as shown in the table, in 1923. Four months after this course of vaccine, which consisted of only five doses, a cold appeared and was relieved on the second day after an initial dose of the mixed vaccine. In 1924, following the vaccine, the patient had two slight colds which were evidenced chiefly by swollen nasal mucous membrane and sneezing. In addition to the usual mixed vaccine, an initial dose of Staphylococcus pyogenes aureus was given, following which in both instances all symptoms were relieved the next day. Following the preventive vaccine in 1925, the patient had three colds in the succeeding two-year period. The first cold appeared ten months, the second one fifteen months and the third one nineteen months after the preventive vaccine. Each cold was relieved within three days after an initial dose of the mixed vaccine without any associated bronchitis or

asthma. In 1927, two months after the preventive treatment, the patient had a cold which promptly cleared up following the initial dose of Streptococcus nonhemolyticus salivarius; this organism was given because it was prevalent at the time, but was not present in the preventive vaccine which the patient had been given.

Patient No. 2 is a female of middle age, a school teacher who had been subject to frequent colds for years. In the winter of 1921, during a period of six months, she had three colds, each of which was relieved in a day or two following a dose of the mixed vaccine. In 1922 she was given the preventive vaccine and during the succeeding three-year period she had only five colds. The first cold in 1922 appeared five months after the preventive treatment, and it was not relieved until she had been given three doses of the mixed vaccine. The second, third and fourth colds came one year, eighteen months and twenty-six months, respectively after the preventive vaccine, and each of them was relieved two days after an initial dose of the mixed vaccine. The fifth cold appeared two months after the previous one and did not disappear until after two doses of the vaccine had been given.

Patient No. 3 is a young man who for years had been subject to attacks of asthma at any time of the year. Following the preventive vaccine in 1922, he was free from asthma for a year, but at the end of this period he had an attack which promptly disappeared during the preventive treatment of 1923. After the 1923 course of vaccine, he was free from asthma for sixteen months, then he began to have slight asthmatic symptoms which were relieved by another course of preventive vaccine in 1925. Following the 1925 treatment, he was well for a year when he had a severe asthmatic attack and the vaccine again seemed to benefit. Two months after the preventive vaccine in 1926 he had a severe cold which his local physician diagnosed as "grippe," after this he was free from colds and asthma for ten months. In 1927, following the vaccine, he was well for a year. In this case it would seem that the vaccine had both curative and preventive value in the several instances that it was given, with the exception of the attack of grippe which it did not prevent. At this time it might be well to call attention to the following facts, namely, that some patients have had an attack of grippe in spite of the preventive vaccine, that some patients, who have had grippe several times before the vaccine was given, state that the vaccine has shortened the attack and made it much lighter than formerly, and that other patients think that the vaccine has prevented grippe.

Patient No. 4 is a young woman, aged twenty-eight years, who has been subject to frequent attacks of asthma at all times of the year since the age of one year. She was sensitive to wheat which was omitted from her diet. An autogenous sputum vaccine, which consisted of Streptococcus mitis and salivarius, was given, and for a year the patient was well with the exception that when she ate any wheat food she had asthma. The following winter the patient had four colds and asthma with each one; therefore, she was given the preventive vaccine in 1925 and during the succeeding fourteen months she had no asthma and only very slight colds. Following the vaccine in 1926 she was free from colds and practically free from asthma for nine months, then the asthma gradually returned and an autogenous sputum vaccine was given. This patient is presented to show the advisability of testing the patient for protein sensitivity and the necessity of avoiding any protein to which there is sensitivity and the importance of using autogenous vaccines in prolonged colds, bronchitis and asthmatic attacks before the anticold vaccine should be used.

Patient No. 5, a young man, had averaged four or five colds each winter for years and each cold was accompanied by asthma. Following the preventive vaccine in 1920 he was free from colds and asthma for nine months, at which time, in the month of August, both returned and another preventive course of vaccine was given (1921), after which the patient had no colds or asthma for a year, and then he had a severe cold and asthma, this was in the month of August, as was the previous cold and asthmatic attack. This time the preventive vaccine did not benefit, therefore, the patient was retested and found to be sensitive to ragweed pollen. Since the patient had had several attacks of asthma with constant bronchitis, an autogenous sputum vaccine was given and relief promptly followed the first few doses, the vaccine was a pure culture of Streptococcus fecalis. During the next two years the patient was given ragweed pollen treatment and was free from asthma, and for two years more without any treatment he remained well. In the fall of 1927 the patient again began to have colds and asthma, therefore, the preventive vaccine was given and for the succeeding year no colds or asthma developed.

This patient is similar to the former in that the importance of doing skin tests and of giving autogenous vaccines is evident, and, in addition, the necessity of giving pollen treatment when indicated. Since the mixed vaccine, which contained Streptococcus fecalis along with other varieties did not benefit, whereas a vaccine of fecalis alone did promptly relieve, this case would seem to illustrate specificity since the total quantity of both vaccines was alike, and the only difference was that in the same dosage there was six times the quantity of fecalis in the autogenous vaccine as compared to the mixed vaccine.

Patient No. 6, a woman, aged thirty-one years, had been subject to paroxysmal attacks of asthma for years with the exception of the summer period. In 1923, since she was having a prolonged attack of asthma with morning expectoration, she was given an autogenous sputum vaccine, for six doses, during which time she became well and remained so for three months when she had another attack of asthma. In 1924 she was given six doses of the preventive vaccine and during this time the patient was free from asthma and remained free for eight months. In the latter part of 1924 she was given another course of the mixed vaccine for six doses, with freedom from asthma for ten months. In 1925 there was freedom for fourteen months following a full course of the vaccine, in 1926 she was free for ten months and in 1927 she was free for thirteen months, furthermore, during each series of vaccine the patient rapidly became free from the asthma which she was having at the beginning of each course of treatment. Therefore, in this case, whereas following the autogenous vaccine the patient was free from an attack of asthma for only three months, following each of four courses of preventive vaccine, the patient was free for from eight to fourteen months and the vaccine seemed to relieve each attack as well as did the autogenous vaccine.

Patient No. 7 is a woman, aged fifty-one years, who had been subject to frequent colds and frequent attacks of grippe all her life. Following the preventive vaccine in 1925 she had one cold which appeared two weeks after the course of vaccine was completed. As with other patients already mentioned, Streptococcus hemolyticus subacidus, although prevalent was not present in the preventive vaccine which was given to her, she was given an initial dose of the subacidus vaccine following which she was much better and after a second dose there was relief in two days. Following the preventive vaccine, in 1926, the patient had two colds, one appeared five weeks and the other seven months after the vaccine. Following two

doses of Streptococcus hemolyticus Type I the first cold was relieved; this vaccine was given because this type of streptococcus was prevalent at the time but was not present in the preventive vaccine with which the patient was treated. Following the vaccine in 1927 the patient had two colds, the first one came five weeks and the other came six months after the completion of the treatment. A dose of the mixed vaccine did not benefit the first cold, but in three days relief followed the same quantity of a vaccine of Streptococcus salivarius; this was given because it was prevalent at the time but was purposely omitted from the patient's preventive vaccine. The second cold subsided on the second day after a dose of the mixed vaccine which contained the salivarius organism.

Therefore, in this case the frequency of colds, to which the patient was subject, was reduced by more than one-half and she had none of her usual grippe attacks. Two colds were relieved in two days following an initial dose of the mixed vaccine. One cold was not benefited by the mixed vaccine, but was promptly relieved following a dose of Streptococcus salivarius, and the other two colds seemed to be cured by doses of Streptococcus subacidus and hemolyticus Type I, respectively, these three instances would seem to illustrate specificity.

Patient No. 8, a girl, aged fifteen years, had been subject to frequent colds and attacks of asthma for years and some winters she would have an attack of asthma every one or two weeks. Following the preventive treatment in 1924 she was free from asthma for so long, namely three years, that in 1926 when she did have a cold and asthma only four preventive treatments were given rather than the usual eight or nine. Three months after this short series of preventive treatments she had a cold and asthmatic attack and eight months later she had a cold, in both instances prompt relief followed one dose of the mixed vaccine. In 1927 the patient was given the regular course of preventive treatment. During the treatment she had a cold, and from her sputum was isolated Streptococcus infrequens and hemolyticus Type I, two months later she had an attack of asthma which was relieved on the day following an initial dose of the mixed vaccine, and at this time her sputum contained Streptococci infrequens, anginosus and ignavus, all of which were present in the vaccine. One month later still she again had asthma which was not benefited by the mixed vaccine and, since her sputum contained only Streptococcus infrequens, she was given a dose of a vaccine containing only this organism, following which there was prompt relief on the next day. These instances would seem to indicate specificity among the varieties of streptococcus in the treatment of colds and asthma in this particular case.

Patient No. 9, a female, nurse, aged thirty-four years, had had frequent attacks of asthma for five years, she also had frequent colds and the asthma was worse with the colds. In 1922, since she was having a prolonged attack of asthma, she was given an autogenous sputum vaccine consisting of streptococci; while this vaccine was being prepared, however, she was given a dose of the mixed vaccine without benefit. Following one dose of the autogenous vaccine, there was definite improvement, this would seem to indicate a specificity among the streptococci. Since she was free from asthma after four doses of the autogenous vaccine she was then, in 1923, given the preventive vaccine, following which she was free from asthma and had no colds of any account for over two years. Since the last course of vaccine, in 1925, the patient has been free from colds and asthma.

Patient No. 10, a young woman, a telephone operator, had been subject to colds frequently for many years and during the last year she had had

attacks of asthma with colds. In 1924 she was given the preventive vaccine, following which, for the succeeding thirty months, she was practically free from colds and asthma, in that she had very slight attacks at infrequent intervals. In 1927 the preventive vaccine was given again and two weeks after its completion the patient had a grippe cold. A dose of the mixed vaccine did not benefit, but following a dose of an autogenous sputum vaccine the patient was relieved in two days. Since the autogenous vaccine contained Streptococcus fecalis and equi, this would seem to be another instance of specificity.

Patient No. 11, a middle-aged woman, had been subject each year to three or four attacks of asthma, always with a cold, for seventeen years, with the exception of one year when she was free following influenza. Following the preventive vaccine in 1920 she was free for nearly two years, when she had a cold and an attack of asthma from which she recovered in two days after the first dose of preventive treatment in 1922. After completion of the vaccine she had no more colds or asthma until 1924, when the vaccine again relieved her, but only three treatments were given at this time. In 1926 the patient returned with a cold and asthma and again an initial dose of the vaccine was followed by rapid relief; this time four doses were given and she remained free for twenty-one months, when she had another attack which was relieved in two days after one dose of the vaccine. This is the only case where so few preventive doses of the mixed vaccine were followed by long periods of freedom from colds and from asthma.

Patient No. 12, a middle-aged woman, for years had been subject to frequent colds and to a continuous wheeze, cough and expectoration. Because she was having continuous wheezing, cough and expectoration she was given an autogenous sputum vaccine, during the administration of which she became free from the chronic symptoms but she continued to have frequent colds. In 1925, four months after the completion of the autogenous vaccine, she was given the preventive vaccine and she was free from both colds and asthma for six months when she had a cold and a return of the cough, expectoration and wheezing. Again she was given an autogenous sputum vaccine, after a few doses of which she became well and remained so for one year. In 1925 the patient had a return of colds and asthma so that the preventive vaccine was again given. The patient stated four months later that she was very well, but was having slight wheezing at times with some expectoration. Again an autogenous vaccine was given, following which she was well for over a year and during the second year she had only slight colds and slight wheezing but no real colds or asthma. Although it is impossible to state what kind of vaccine gave the most relief, it is evident that desirable results followed in two separate instances when both kinds of vaccine were given, and in such cases, where there is evidence of chronicity, or incomplete relief from the mixed vaccine, an autogenous vaccine is indicated and the combination seems to give better results than either alone.

Patient No. 13, a middle-aged man, had been very susceptible to colds for years. In 1925 he was given the preventive vaccine and had no colds for nine months and the cold at that time was relieved in two days by an initial dose of the mixed vaccine. He had a second cold three months later, and this one also promptly disappeared following a dose of the mixed vaccine. In 1926, following the preventive vaccine, the patient had two colds in the succeeding two years. The first cold was sixteen months and the second one twenty months after completion of the preventive vaccine, and both were relieved on the second day after a dose of the mixed vaccine.

Patient No. 14, a girl, aged six years, had been subject to colds and asthma with colds since infancy. Following the preventive treatment in 1924 she was free from asthma and colds for eleven months, and the cold that she had at the end of this period was relieved without asthma after a dose of the mixed vaccine. Following the preventive treatment in 1926 she was free from colds and asthma for a year. During the next two years the preventive vaccine was not given and the patient had many colds and asthmatic attacks.

Patient No. 15, a young man, had been subject to four or five colds a year, and during the last two years he had had asthma with the colds. Following the preventive vaccine which was given in 1920 the patient had one cold, from which he recovered without asthma on the day following an initial dose of the mixed vaccine. Following the treatment in 1921 he had slight wheezing two months after the treatment, but on the day following a dose of the mixed vaccine he became free. In succeeding years the patient took the vaccine only when he had a cold, therefore, he is presented in Table III as Patient No. 1.

Patient No. 16, a girl, aged eight years, had been subject to colds, attacks of bronchitis, earache and frontal headache, accompanied by fever, for years. She had lived in Texas, Iowa, California and Massachusetts without benefit. Since she was having one of her usual attacks of bronchitis she was given, in 1925, four doses of an autogenous sputum vaccine, during which treatment she became well. The autogenous vaccine contained Streptococcus infrequens, hemolyticus Type III and nonhemolyticus Type III. Following the autogenous vaccine treatment, she was given in 1925 the preventive treatment and she had no more colds or other symptoms when she was last heard from, eighteen months later.

Patient No. 17, a girl, aged four years, had been subject to frequent and severe colds which during the previous two months had caused two attacks of asthma, and for the previous six months she had had a persistent cough and evening temperature of 100° F. She was given a course of the preventive vaccine, following which there was marked improvement and normal temperature. After an interval of two months the course of vaccine was repeated. She was free from colds and asthma for twenty months, then she had a cold and asthma for several days, but on the day following a dose of the mixed vaccine she was relieved. A year later she had another cold and asthma for two days and again she was relieved on the day following one dose of the mixed vaccine.

Patient No. 18, a boy, aged seven years, had had frequent colds with a chronic cough for two winters. Following the preventive treatment in 1925 he had a cold one year later that was cured on the second day after a dose of the mixed vaccine, and he did not have another cold for a second year, and even since then the colds have not been sufficiently serious to require treatment.

Patient No. 19, a boy, aged six years, the son of Patient No. 15, was susceptible to colds, and in 1925 he was given the preventive vaccine, following which he had two colds in the succeeding two-year period. These two colds came two and four months, respectively, after the completion of the mixed vaccine, and both were relieved on the day after an initial dose of Streptococcus subacidus vaccine which was given because this organism was very prevalent at the time, and it was not present in the preventive vaccine that was given to the patient.

Patient No. 20, a young woman, a school teacher, who was a sister to Patient No. 15, had been very susceptible to colds for years. In 1922 she was given the preventive vaccine, following which she had no colds for eight months. Beginning in 1923 she took the treatment only when she had cold, so that this patient is presented in Table III as Patient No. 2.

In Table III are presented 10 patients, who were treated for three years or more only when they had a cold and the treatment consisted of 3 minims or 0.2 cc. of the mixed vaccine which was composed of those varieties of streptococci which were most prevalent at that time; the bacterial count was approximately 100 million per minim.

TABLE III.—NUMBER OF COLDS PER YEAR IN PATIENTS RECEIVING VACCINE ONLY DURING COLDS (NO PROPHYLACTIC VACCINATION).

	1921.	1922.	1923.	1924.	1925.	1926.	1927.	1928.
Patient 1	..	3	3	4	3	3	3	4
" 2	..	..	5	4	4	5	5	
" 3	1	1	1	1	4			
" 4	..	1	1	1	1	1	1	1
" 5	..	..	4	1	1	3	..	2
" 6	..	..	3	1	1	1	2	
" 7	2	..	2	4	3			
" 8	..	..	4	4	4	4		
" 9	..	..	..	1	2	3	1	
" 10	..	..	..	..	..	3	3	

Patient No. 1 was presented in Table II (Pt. No. 15) as having had preventive vaccine treatment in 1920 and 1921 and the results of such treatment were discussed. During the years 1922 and 1928, inclusive, it is noted in Table III that this patient averaged to have three colds during each of the seven years or a total of twenty-three colds. In nineteen instances one dose of the mixed vaccine was followed by relief in two days and in the four other instances one dose resulted in benefit and a second dose one week later was followed by relief; in only one instance did asthma occur.

Patient No. 2 was presented in Table II (Pt. No. 20) has having had preventive treatment in 1922 only. During the years 1923 to 1927, inclusive, as noted in Table III, this patient had a total of twenty-three colds; she had four colds during each of two years and five colds during each of three years. In twenty-one instances prompt relief on the next day followed one dose of the vaccine and in the other two instances a second dose was given before complete relief was obtained.

Patient No. 3 is a young woman who has always been subject to frequent heavy colds and during the previous six years she had had asthma with colds. During the years 1921 to 1924, inclusive, the patient appeared for treatment only when she had a bad cold with asthma for two or three days. In three of the four instances there was relief on the first day following the mixed vaccine, and in the other instance benefit followed the first dose and relief followed a second dose of the vaccine a week later. In 1925 the patient appeared for treatment for four colds, and each time there was relief on the first or second day following one treatment with the vaccine.

Patient No. 4, a middle-aged man, was subject to one cold a year, and for seven successive years each cold was cured in one to three days following one dose of the mixed vaccine.

Patient No. 5, a middle-aged woman, had been subject to colds and asthma for ten years. In 1923 she was treated for four colds, two of the colds were not relieved until a second dose of the mixed vaccine was given, the other two colds subsided on the first or second day following one dose of the vaccine. In 1924 and 1925 she was treated for one cold each year, and each cold promptly subsided after one dose of the mixed vaccine. In 1926 she was treated for three colds, two of the colds were promptly relieved on the second day by one dose of the vaccine and the other one was not relieved until after a second dose. In 1928 she was treated for two colds and both times a second dose of the vaccine was given before she got relief. With all of the colds for which the patient was treated she also had asthma.

Patient No. 6 is similar to the former in that she presented herself for treatment only when she had asthma with her colds. In 1923 she had three colds with asthma and in each instance there was relief within three days after a dose of the mixed vaccine. During the next three years she was treated for one cold with asthma each year, and each time she was relieved by the second day after one dose of the vaccine. In 1927 she was treated for two colds with asthma and each time, as before, relief followed one dose of the vaccine.

Patient No. 7, a young man, had been subject to vasomotor rhinitis and frequent colds for years. During the years 1921 and 1923 the patient was treated for two colds each year, in three instances a second dose of the mixed vaccine was required before complete relief was realized, but in the other instances prompt relief followed one dose of the vaccine. In 1924 he was treated for four colds, two required two doses of the vaccine and the other two colds rapidly subsided after one dose of the vaccine.

Patient No. 8, a middle-aged man, who was subject to colds which occasionally went into his chest, was treated for four colds in each of the four years, 1923 to 1926, inclusive. Each year three of his colds were cured after one dose of the mixed vaccine, but each year one cold was not relieved until after a second dose of the vaccine was given.

Patient No. 9, a middle-aged woman, was subject to "asthma colds" for six years. In 1924 a dose of the vaccine was followed on the second day by relief. In 1925 one cold was relieved in a day or two after a dose of the mixed vaccine, for another cold in the head she was given a dose of Staphylococcus pyogenes aureus without benefit, and a week later, following a dose of the mixed vaccine, the cold was well in two days. In 1926 she was treated for three colds, from all of which there was recovery by the second day following one dose of the mixed vaccine without any symptoms of asthma. The following year the patient was treated for one cold which likewise promptly disappeared after one inoculation.

Patient No. 10, a young man who was subject to head colds, was treated for three colds in 1926 and three in 1927. Four of the six colds were relieved on the second day following one dose of the mixed vaccine, but the other two were not relieved until a second dose of vaccine five days later was given.

The following patients who have already been discussed might be included in this table, namely Patients 1, 2, 7, 8 and 13 who were

presented in Table II and Patient 1 in Table I. These 6 patients were treated for numerous colds and the results have already been mentioned in the discussion of the respective patients in Tables II and I.

During the years 1921 to 1925, inclusive, 42 patients other than any appearing in this paper were treated with the mixed vaccine one or two times when they had a cold. Ten of these patients were asthmatics and were treated once for a cold, 4 were asthmatics who were treated for two colds, 10 were hay fever patients and were treated once for a cold, 2 others were hay fever patients and were treated for two colds, 10 were normal cases who were treated for one cold and 6 others were normal cases who were treated for two colds. All of this group of 42 patients were relieved of their colds in from one to three days' time following one dose of the mixed vaccine.

Summary. *Table I.* In this Table are discussed 19 of 97 patients who were presented in a former paper[1] and who received preventive treatment for colds with vaccines consisting of the varieties of streptococci that were prevalent during the periods of treatment. This particular group of patients was selected for the present paper because they presented themselves for further treatment whenever they had a cold.

This group of patients was treated with mixed streptococcus vaccine, as described above, for a total of thirty-seven colds. Thirty-one of these acute colds rapidly and promptly subsided following an initial dose of the mixed vaccine and six colds were not benefited.

Two of the six colds that were not benefited by the mixed streptococcus vaccine promptly subsided following the same dose of an autogenous streptococcus vaccine; this would seem to illustrate specificity among the varieties of streptococci in the treatment of colds in these two instances.

Another definite case illustrating specificity is that of Patient 12, whose asthma on two different occasions was not benefited by the mixed streptococcus vaccine but both times there was rapid improvement following treatment with a vaccine of Staphylococcus pyogenes aureus.

Five other instances are of interest in that one of the prevailing varieties of streptococci was omitted from the preventive vaccine that was given and a cold which developed shortly afterward was promptly relieved following a dose of vaccine which contained only the omitted variety of streptococcus. These 5 instances concerned Streptococcus subacidus with Patients 1, 3 and 24 in 1925 and Streptococcus hemolyticus Type I with Patients 1 and 9 in 1926. Under the circumstances which prevailed in these 5 instances, the result would indicate specificity among the varieties of streptococci.

Table II. The twenty patients in this table had more or less preventive vaccine treatment. Fourteen of them were included in

the 87 referred to in the discussion of the previous paper[1] but were not included in the tables of that paper.

This group of patients was treated with the mixed streptococcus vaccines as described above for a total of forty colds. In 33 instances the cold promptly and rapidly subsided following an initial dose of the vaccine and in 7 instances the colds were not benefited.

Three of the seven colds that were not benefited by the mixed streptococcus vaccine promptly subsided following the same dose of an autogenous streptococcus vaccine; in one instance the autogenous sputum vaccine was Streptococcus infrequens alone, in another it consisted of Streptococcus fecalis and equi and in the third case the variety was not determined. These three instances would seem to illustrate specificity among the varieties of streptococci in the treatment of colds.

Five other instances are of interest in that one of the prevailing varieties of streptococci was omitted from the preventive vaccine that was given and a cold which developed shortly afterward was promptly relieved following a dose of vaccine which consisted only of the omitted variety of streptococcus. These 5 instances concerned Streptococcus subacidus with Patients 7 and 19 in 1925, Streptococcus hemolyticus Type I with Patient 7 in 1926 and Streptococcus salivarius with Patients 1 and 7 in 1927. Under the circumstances which prevailed in these 5 instances, the result would indicate specificity among the varieties of streptococcus in the treatment of colds.

Table III. In Table III are presented 10 patients who were not given the preventive vaccine treatment but were treated with the mixed streptococcus vaccines only when they had a cold. This group was treated for a total of one hundred and twenty colds. In 96 instances prompt relief followed one dose of the vaccine but in the remaining 24 instances the patients returned a week later for a second inoculation; therefore, these 24 instances may be called failures from the curative standpoint. Forty-two other patients were treated for a total of fifty-two colds during the period 1921 to 1926 inclusive with prompt relief.

Conclusions. A vaccine consisting of the varieties of streptococci that are most prevalent at certain periods seems to be beneficial in the relief or cure of acute colds that occur during that period.

The same vaccine used as a preventive was not always successful, probably because in many instances a cold or asthmatic attack which followed its use seemed to be due to a variety of streptococcus not present in the vaccine.

No attempt was made to prove specificity among the varieties of streptococci; nevertheless, in numerous instances specificity seemed to be quite evident.

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SOME EXPERIMENTS IN INTRACRANIAL PRESSURE IN MAN DURING SLEEP AND UNDER CERTAIN OTHER CONDITIONS.

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Mosso, in 1881, wrote a treatise on "The Circulation of the Blood in the Brain of Man." In this book, he attempts to show that sleep is associated with a decrease in the intracranial pressure which he thought was due to a cerebral anemia. His work is based on experiments on three patients and the tracings illustrating his theory seem to cover too short a period to be convincing. His apparatus resembled our own, but was somewhat more complicated and not so sensitive for, obviously, it did not always record falls in the intracranial pressure (see page 137, Fig. 53).

Since Mosso's time, the anemic theory of sleep has been a popular one with physiologists. This theory has been supported by such workers as Tarchanoff, Villemin, Hill and Howell. On the other hand, there have been workers who have taken the view that sleep was caused by cerebral congestion—among these are Kennedy (1877), Langlit, Regard, Czerny and Shepard. There are other, perhaps less popular, theories or at least partial explanations of sleep among which may be mentioned the neuronic theory of Cajal and Duval. The number of these theories and the prevalence of the anemic theory of sleep seem to depend on the lack of direct observation or experiment upon the brain itself during sleep. Howell, for example, assumes that, since the bloodvessels of the extremities are dilated during sleep (as he has shown by plethysmographic experiments), the bloodvessels of the brain must be relatively empty.

Some years ago, on the service of Dr. Foster Kennedy at Bellevue Hospital, we had the opportunity of making direct observations on 2 cases of brain hernia during sleep. During the past year we have studied 2 more cases on the same service. In a fifth case we have studied Jacksonian epilepsy in a patient with a brain hernia. In 2 of these cases we have made observations on the intracranial pressure under various other conditions. These 2 cases had a

subtemporal decompression with a cerebral hernia over which the dura had been cut and left unsutured.

We have obtained 19 tracings taken during sleep; 13 were made during natural sleep and 6 while the patients were under the influence of hypnotics. These all show that the intracranial pressure rises as the patient falls asleep—this increase of pressure being maintained during sleep—and falls again to its normal level when the patient awakes. In our cases the process of falling asleep was a gradual one, the intracranial pressure rising slowly for a matter of ten minutes before the patient was sound asleep and before the curve reached its highest level. On the other hand, awakening is effected in a shorter time and is accompanied by a more sudden change of the pressure.

In some of the tracings obtained under ideal conditions, where the patient was aroused and again fell asleep, we have found a rhythmic fluctuation in the upward tendency of the curve as the patient falls asleep. We feel that this has some significance in the theory of sleep which we propose.

Two of us have made observations on the fundus oculi during sleep, while the patients were under the influence of paraldehyde, the pupils having previously been dilated with homatropin. No change in color of the fundus or in size of the retinal vessels could be seen as compared with their appearance while awake.

During sound sleep, the respirometer shows the thoracic breathing to be much deeper than when the patient is awake.

Howell's plethysmograph tracings of the arm (*Text Book of Physiology*, page 266) have a remarkable resemblance to our tracings obtained from the brain during sleep. We believe that the change in volume shown in these two series of tracings is attributable to the same phenomenon, namely, increase and decrease of blood volume.

Figure 1 illustrates the apparatus, which consists of a closed air tambour system under a positive pressure of about 12 mm. of mercury. One tambour was strapped and bandaged over the brain hernia. The other was attached to a light-weight pointer, which registered on a smoked drum the changes of intracranial pressure due to pulse, breathing, sleep and the other conditions we are about to describe. The drum was regulated so that it made a complete revolution in twenty minutes. At times the drum was stopped so as to allow observation over a longer period of time. In most cases our tracings represent one complete revolution of the drum, although they have not all been photographed to the same scale. In some cases a clear photographic reproduction could not be obtained, so that it was necessary to trace these on paper placed over the original. This tracing was then easily photographed.

Figures 7, 8 and 9 demonstrate the lowering of the intracranial pressure in one of our patients on being aroused.

Figures 10, 11 and 12 are similar tracings on another patient. In Figure 11, a pneumographic tracing was made at the same time.

Figure 15 shows scalp control.

Figure 16 shows a sleep curve (Brady) while the patient was sitting in a chair. After he was aroused fully he was given an inhalation of 5 minims of amyl nitrite. Later jugular compression was applied for periods of ten seconds. Note here that the fall in ntracranial pressure on awakening is much greater than in the tracings taken when the patient was lying down.

Figure 18 shows a marked sudden rise of intracranial pressure during the inhalation of 5 minims of amyl nitrite and for about one minute after the inhalation was stopped. The pressure then fell rather rapidly. During the rise in the curve the blood pressure dropped from 94 systolic, 60 diastolic to 80 systolic, 48 diastolic. By the time the intracranial pressure had returned to normal the blood pressure was normal.

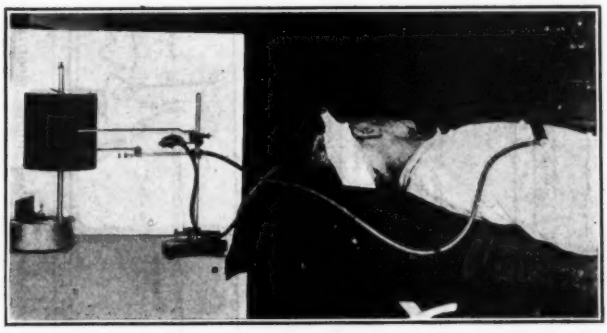
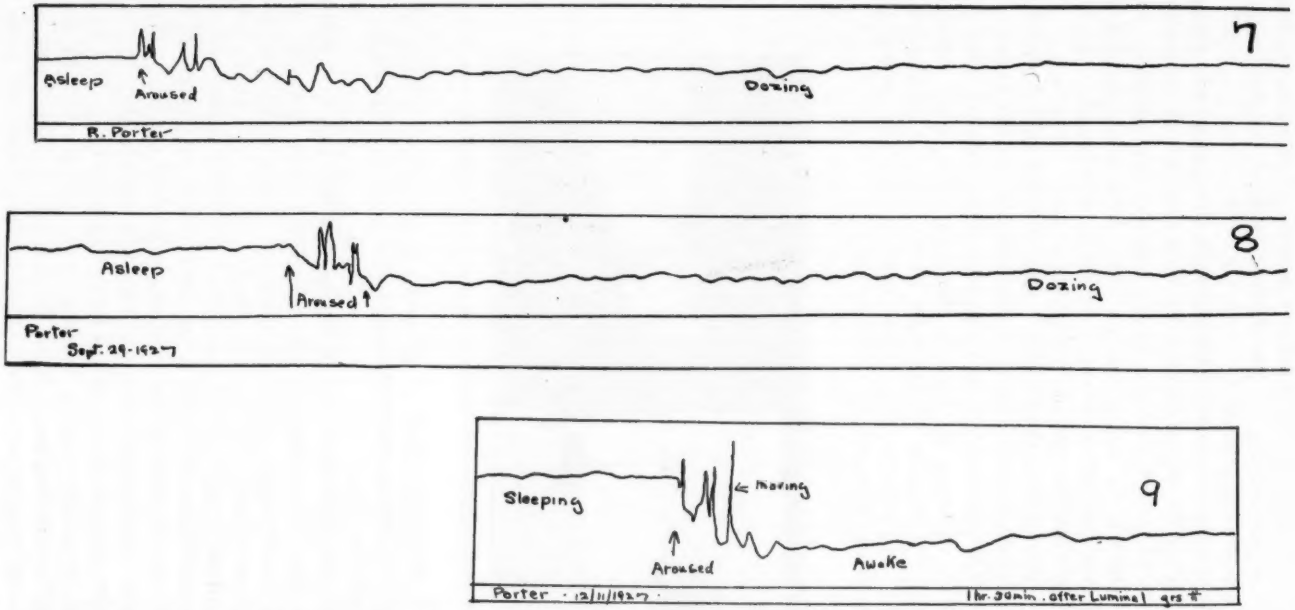


FIG. 1.—Apparatus applied over the brain hernia with the patient lying down.

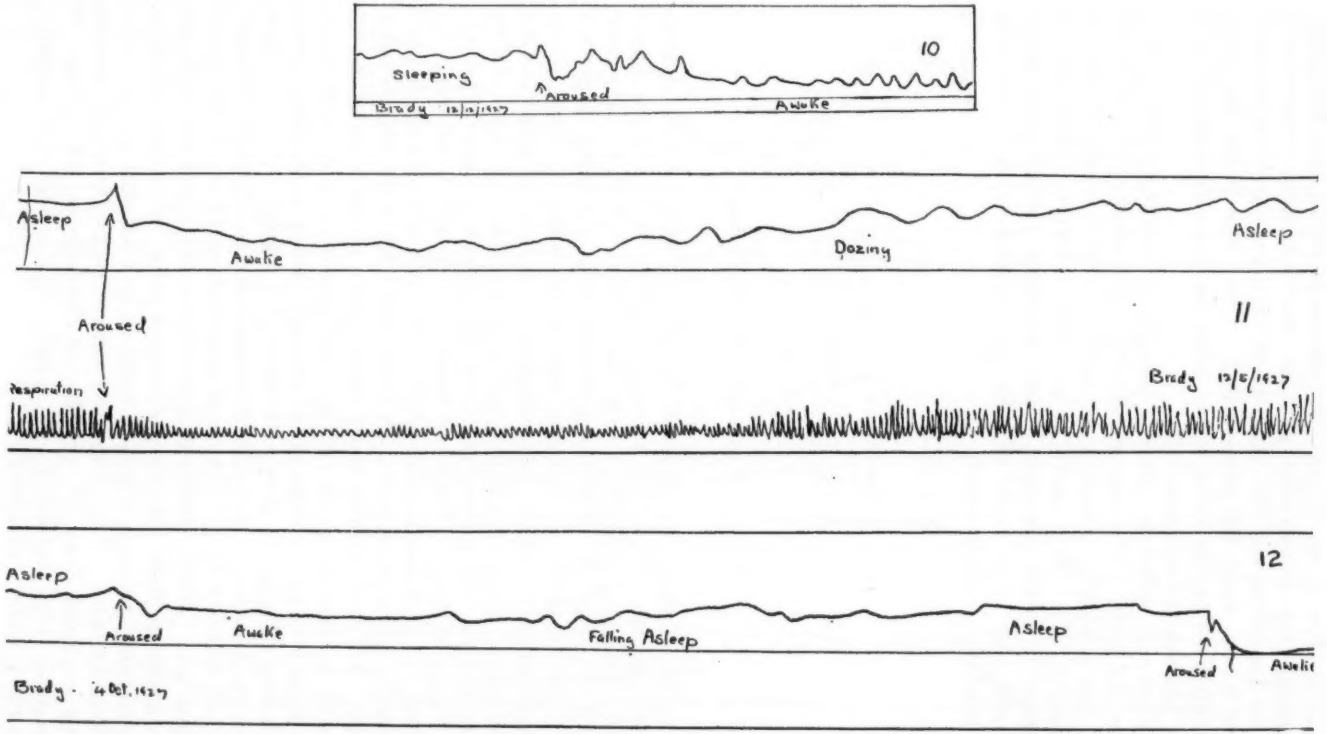
Figure 19 shows the effect of glonoin $\frac{1}{160}$ gr. given sublingually. The effect lasted about twenty minutes with a corresponding fall in blood pressure.

Figure 21 was made on a case of Jacksonian epilepsy with almost continuous fits. Gas-oxygen-ether anesthesia was induced and maintained for one hour. The fits stopped in about two minutes and did not recur until the patient awoke, about five hours later. At the end of thirty minutes of anesthesia the intracranial pressure reached its maximum, this level being maintained for the rest of the hour and it was the same as the level at the peak of the fits. When the anesthetic was stopped, the pressure fell considerably but was still not quite normal at the end of forty-five minutes. The blood pressure fell from 136 systolic, 80 diastolic to 122 systolic, 80 diastolic during the anesthesia. Figure 22 shows that chloroform kept the intracranial pressure at a level equal to that during the peak of the fit. Chloroform was given about thirty minutes, and five



FIGS. 7, 8 and 9.—The difference between the intracranial pressure during sleep and while awake. The first part of each curve shows the pressure during sound sleep—the uneven part of the curves is caused by the process of being awakened. When the patient is fully awake the pressure continues at a low level. In the last portion of Fig. 7 the pressure is seen to rise gradually as the patient falls asleep again.

NOTE.—On account of insufficient space it has been necessary to omit a number of figures that were originally included.



FIGS. 10, 11 and 12.—Three more sleep curves. Fig. 11 shows the respirometer reading at the bottom. Fig. 12 also shows two periods of sleep.

minutes after it was stopped the patient began to have fits again, although the intracranial pressure had not fallen appreciably. Ether anesthesia was then started and the fits stopped, but the pressure in the head fell considerably. Ether was given for thirty minutes. After the ether was stopped the pressure again fell and the fits recurred one hour later.

Figure 23 shows the effect of morphin given subcutaneously in a dose of $\frac{1}{4}$ grain. Five minutes after the injection the pressure began to rise gradually, reaching its maximum at the end of twenty minutes. The effect lasted about eighty minutes. There was no change in blood pressure. Since morphine increases the intracranial pressure, it would be safer not to administer it for the relief of headache in brain tumor.

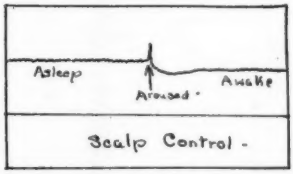


FIG. 15.—Scalp control taken during sleep.

Figure 30 shows the effect of $2\frac{1}{2}$ grains of caffeine sodiobenzoate intravenously. The pressure began to fall at the end of one minute and reached its minimum at the end of three minutes. The effect gradually wore off, lasting about twenty-seven minutes altogether.

Figure 31 shows the effect of 5 gr. intravenously. There was an immediate fall with its greatest effect at the end of three minutes and lasting about twenty-five minutes altogether. In none of these experiments with caffein was there any change in blood pressure.

Figure 42 shows the effect of 2 and 3 minims of adrenalin by vein. There was an immediate fall in pressure, together with a rise in blood pressure and an increase in amplitude and force of the hernial pulsation. These conditions lasted about three minutes and were followed by normal blood pressure and pulsation, but there was a delayed increase of intracranial pressure lasting more than twenty minutes. Figure 41 shows the effect of 4 minims by vein. There was an immediate rise in the intracranial and in the blood pressures, closely followed by an increase of amplitude and force in the hernial pulsation. These conditions lasted five minutes and were followed by a normal blood pressure and hernial pulse, and a delayed rise of intracranial pressure which was still at its maximum at the end of fifteen minutes. With 2 minims intravenously the blood pressure was increased from 100 systolic, 64 diastolic to 124 systolic, 70 diastolic; with 3 minims to 156 systolic, 74 diastolic; with 4 minims to 190 systolic, 110 diastolic.

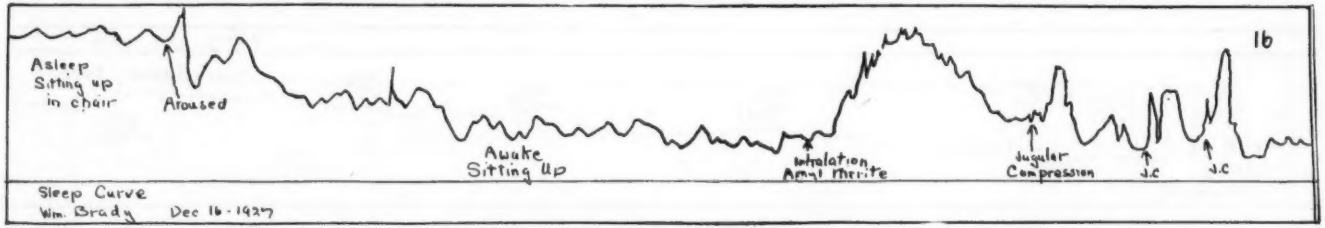


FIG. 16.—A sleep curve made while the patient was sitting up in a chair. This curve shows also the effect of amyl nitrite and jugular compression on the intracranial pressure.

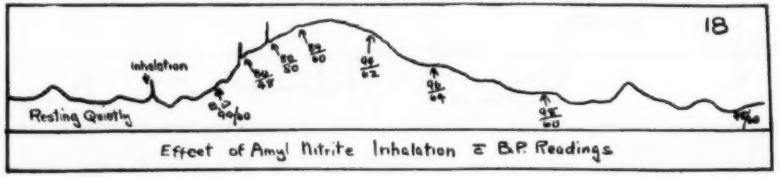


FIG. 18.—The effect of amyl nitrite with blood-pressure readings.

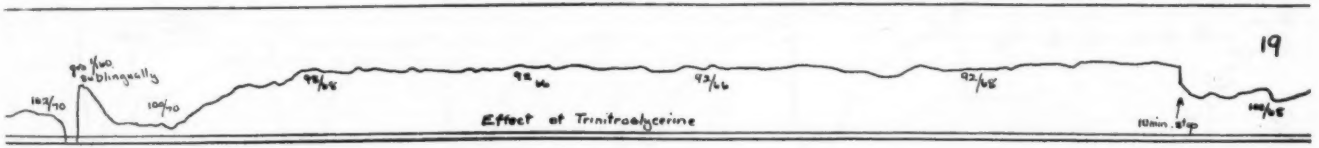


FIG. 19.—The effect of glonoin with the blood-pressure readings.

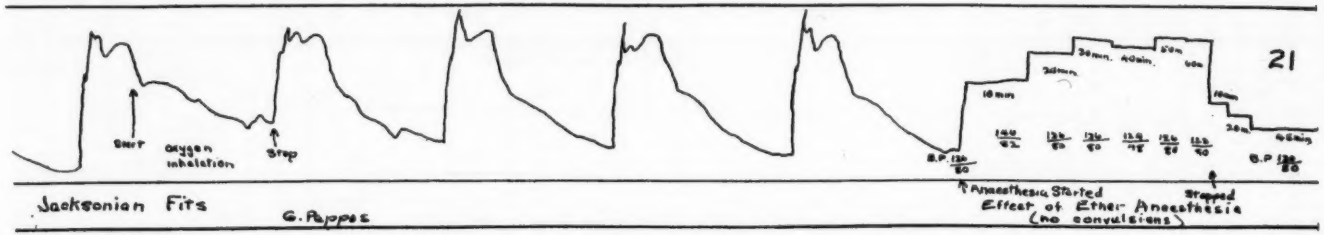


FIG. 21.—The effect of gaso-oxygen-ether anesthesia on the intracranial pressure in a case of Jacksonian epilepsy with almost continuous fits.

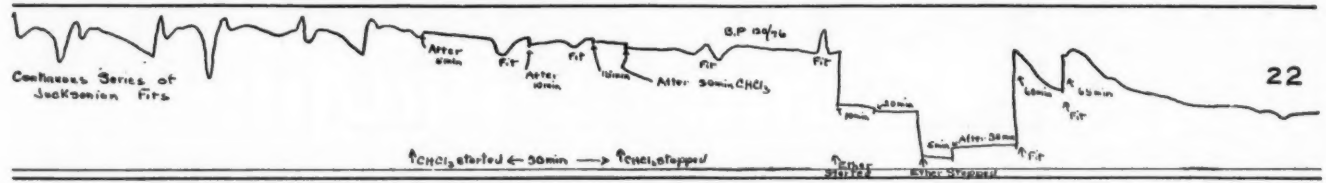


FIG. 22.—The effect of chloroform anesthesia followed by ether, on the same case.

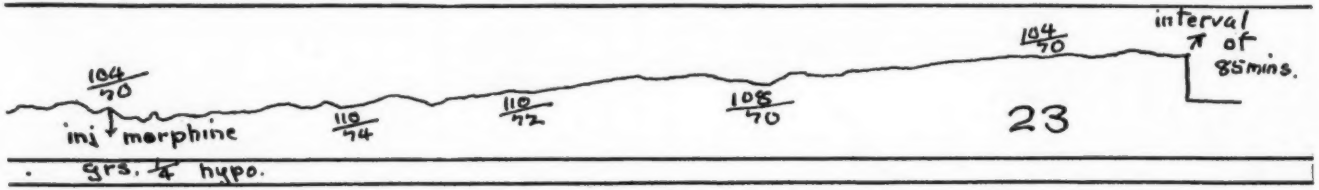
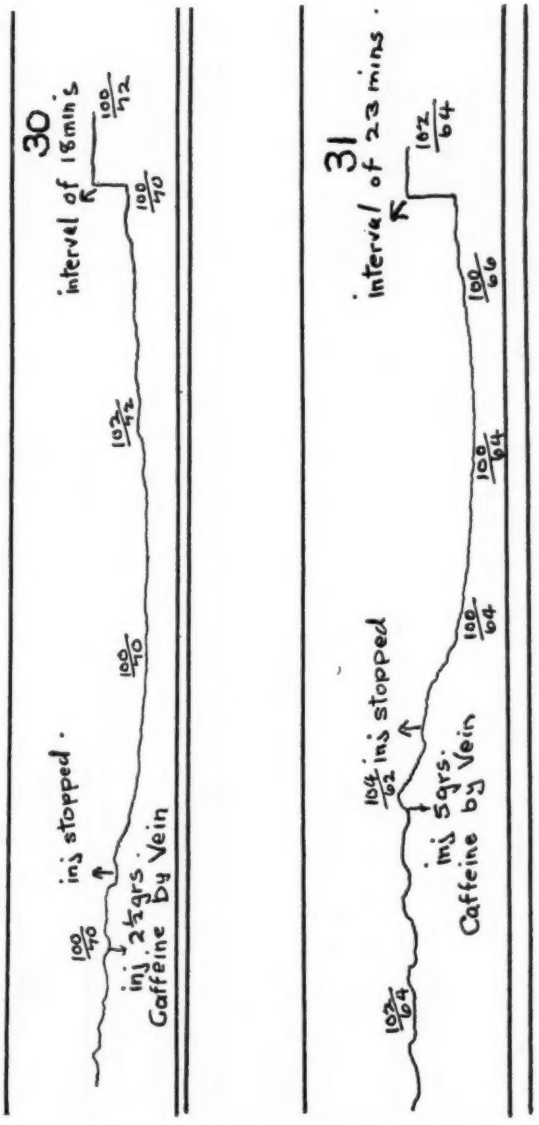


FIG. 23.—The effect of morphine subcutaneously. The tracing covers a period of about eighty-five minutes.

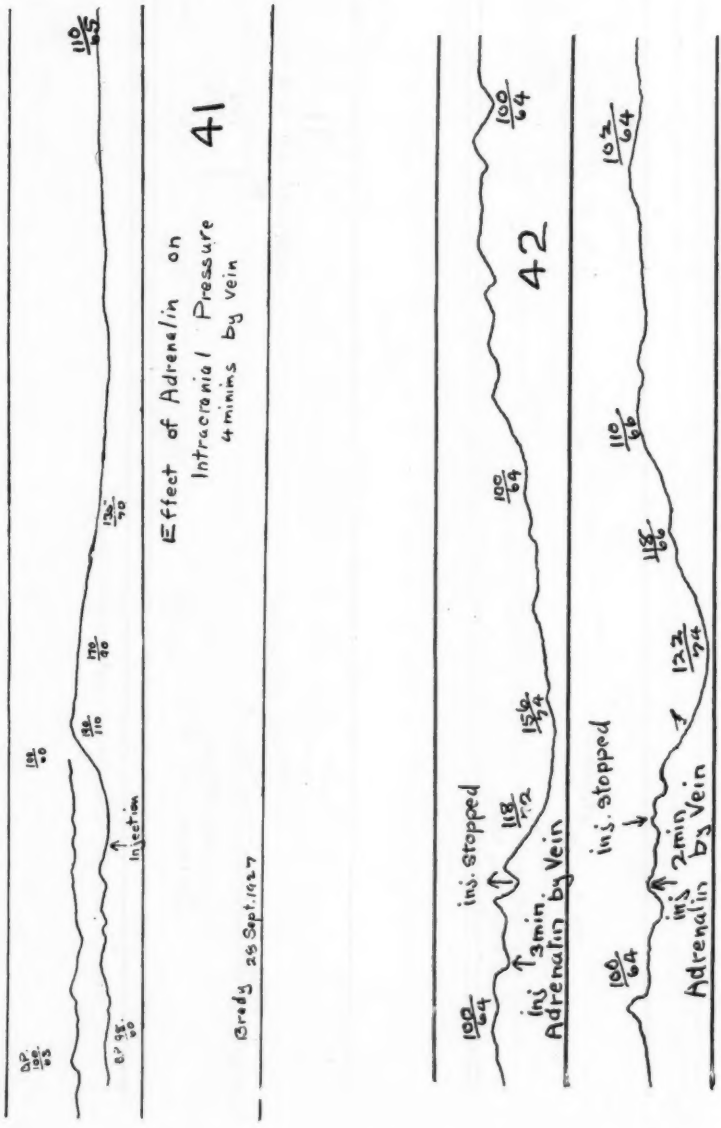
Figure 54 is a tracing of the changes in the intracranial pressure taken during a series of fits in a case of Jacksonian epilepsy. Twenty



FIGS. 30 and 31.—The effect of caffeine-sodio-benzoate intravenously with blood-pressure readings.

minims of paraldehyde were given by vein during the fits with no apparent effect. Hypertonic glucose solution was given by vein on two occasions to this patient. The intracranial pressure showed a

slight fall, but in each instance the fits became more frequent and severe. This patient was later found to have a brain cyst near the hernia.



FIGS. 41 and 42.—The effect of 4, 3 and 2 min. of adrenalin (solution 1 to 1000) intravenously with blood-pressure readings.

Figure 58 shows calibration. The apparatus was applied and a tracing made with the patient (Brady) at rest lying down. The

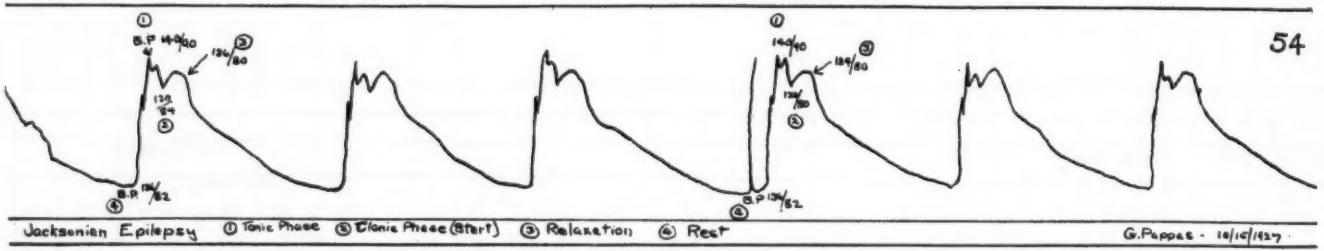


FIG. 54.—Jacksonian fits.

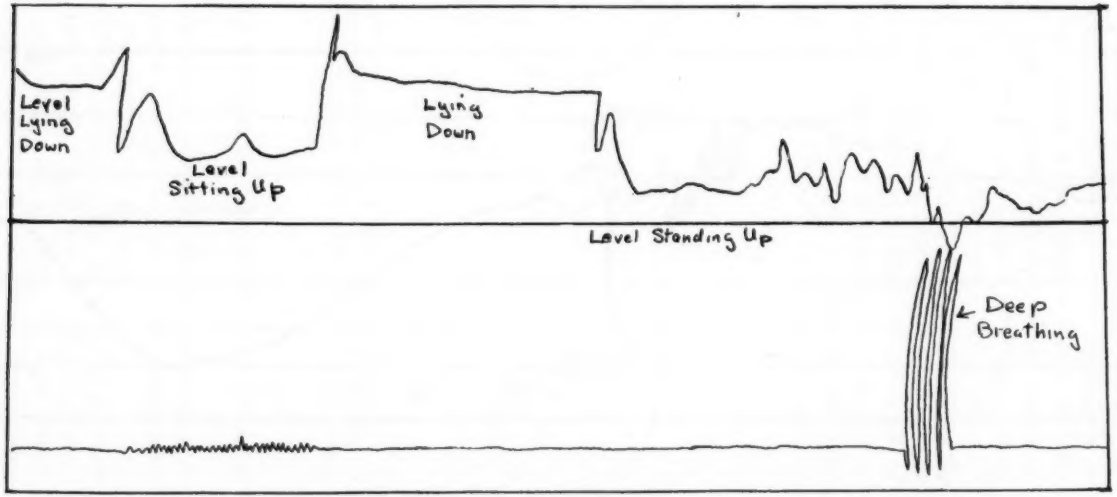


FIG. 56.—Changes of intracranial pressure due to changes in position and to deep breathing.

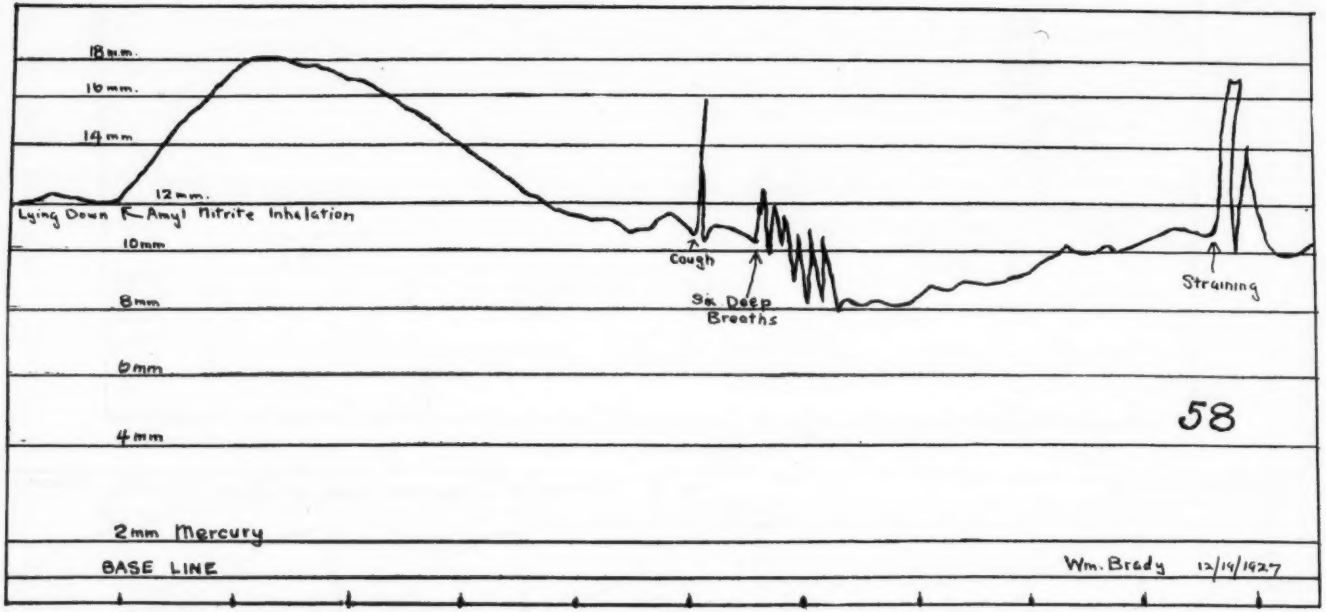


FIG. 58.—Calibration of the apparatus. The black dots at the base represent minutes and the horizontal lines represent each 2 mm. of mercury.

tube was then cut and connected with a mercury manometer (Baumanometer). The air pressure was again reëstablished within the apparatus so that the pointer reached the original level; this pressure was found to be 12 mm. of mercury. Amyl nitrite was then given (5 minims by inhalation), causing a rise equivalent to 6 mm. of mercury. A cough caused a rise equal to 5 mm. of mercury. Deep breathing (6 deep breaths) caused a fall of 3 mm. of mercury. Straining caused a rise of 6 mm. and a secondary rise of 3 mm. of mercury. Each ruled division represents 2 mm. of mercury. The dots along the base represent one-minute intervals of time. A sleep curve, according to this calibration, would mean that the intracranial pressure is raised from about 2 to 6 mm. of mercury, depending on whether the patient is lying down or sitting up when he falls asleep. The difference of pressure in the head between the sitting-up position and lying down is about 4 mm. of mercury.

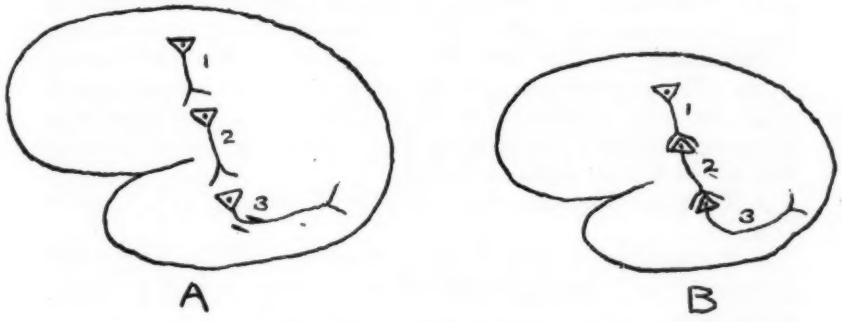


FIG. 59.—*A*, presumable condition of brain during sleep with conduction of impulses blocked because of separation of neurons 1, 2 and 3; *B*, brain in waking state or, under the influence of caffeine, with neurons more closely in contact and passage of impulses facilitated.

Figure 59 is a diagram to illustrate the mechanical effect of dilatation of cerebral capillaries.

Some other tracings were made following the administration of luminal, bromid and chloral by mouth, but these showed no effect on the intracranial pressure within an hour.

Our experiments on the effect of drugs on the intracranial pressure have all been repeated one or more times and the effects demonstrated above have been constant. In addition to these drugs, pituitrin, adrenalin, ephedrin sulphate and hyoscin were given subcutaneously and showed a delayed but prolonged rise in intracranial pressure. Atropin and pilocarpin given subcutaneously caused little change. Hypertonic glucose solution by vein and magnesium sulphate by rectum caused slight fall in intracranial

pressure that was not nearly so great as that produced by caffein. Caffein given subcutaneously caused a definite fall of intracranial pressure that was still present at the end of forty minutes.

A few observations were made with the spinal manometer. The basic spinal fluid pressure with the patient lying down was 150 mm. of spinal fluid. Five minims of amyl nitrite caused a rise to 285 mm. Two minims of adrenalin by vein caused a slow rise to 205 mm.; the blood pressure rose from 105 systolic to 165 systolic. Deep jugular compression for ten seconds caused a rise to 350 mm. With the patient sitting up and his head erect, the pressure rose to 470 mm. Caffeine sodiobenzoate intravenously (2½ grains) caused a fall to 120 mm.

In another patient 3 gr. of caffein sodiobenzoate by vein caused a fall from 155 to 119 mm.

Following these observations, caffein has been used during brain operations at Bellevue Hospital in order to reduce the intracranial tension before opening the dura. Caffein sodiobenzoate has been given intravenously in doses of 6 gr. for this purpose. This principle may also explain why caffein relieves headache due to brain tumors.

Conclusions. 1. The intracranial pressure is increased during sleep. The pressure gradually rises until the patient is sound asleep, when the curve reaches its maximum, and this is maintained at a fairly constant level during sound sleep. On awakening the pressure falls rather rapidly again to normal.

2. There is an increase of the intracranial pressure on lying down (Fig. 56).

3. Partial sleep or drowsy states are associated with a rhythmic increase of the intracranial pressure which is not so high as during sound sleep.

4. Certain drugs which are known to affect the nervous system as sedatives or as stimulants depend in part for their effect upon a hitherto unappreciated mechanical factor, namely, an increase or a decrease of the intracranial pressure. For example, morphin, a sedative, causes an increase of the intracranial pressure, while caffein, a stimulant, produces a fall.

5. The intracranial pressure is, within wide limits, independent of the blood pressure.

6. Our conception of the physiology of sleep, arrived at from a study of our experiments and those of other workers, is as follows:

We believe that the sympathetic center in the brain which maintains vasomotor tone in the vessels becomes periodically fatigued. This results in a vasodilatation of the bloodvessels of the brain, as well as those of the periphery. Accompanying this, as further evidence of fatigue in the sympathetic system during sleep, are the constricted pupil, the slower heart rate, and the decrease of blood pressure. This vasodilatation in the brain would result in one of two things:

(*a*) The brain volume would be increased with a consequent pulling apart of the neurons (diaschisis). This might result in a physiologic interruption of function in the manner suggested by Cajal and Duval when they assumed that the dendrites of the nerve cell were contractile.

(*b*) The pressure of the cerebrospinal fluid within the brain would be increased and especially in the pericellular spaces, thus altering the conductivity of the synapse.

CONVULSIVE STATES.

A Clinical Study of Unusual Phenomena, Etiology, Differential Diagnosis, and Treatment.

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In routine office examinations of the past three years G. A. Young and I have examined over 200 patients in convulsive states. A study of these records reveals numerous facts of interest to any practitioner called to attend a convulsive case.

The examination of a convulsive state demands, because of the grave and severe symptom involved, not only a careful physical and neurologic examination but also complete laboratory studies. The extent of these studies should be determined by a careful analysis of the case history and should include, wherever indicated, Roentgen rays, blood chemistry, metabolic tests, allergy studies, feces analysis, spinal-fluid pressure, cell count, protein estimation, Wassermann test, and Lange gold curve. At times encephalography is necessary. The large majority of the cases here reviewed were hospitalized several days for complete examinations. Sometimes direct observation of the seizures was indicated in order to determine the character of convulsions and to reach an accurate diagnosis.

Of our 200 cases, 124 were classified as essential epilepsy including status epilepticus. Of the remaining 76, 11 cases were hysterical; 9 were listed under traumatic causes; and 56 cases of epileptiform seizures were considered of organic pathogenesis. In this last class were: Brain tumor, 10; brain abscess, 2; cerebrospinal syphilis, 7; encephalitic or meningitic sequelæ, 5; infantile cerebral palsy from birth hemorrhage, 8; cardiovascular disease, 9; organic and toxic of obscure etiology, 11; narcolepsy, 4.

Etiology of Essential Epilepsy. Of various hypotheses with regard to the etiology of essential epilepsy, it seems certain that no single

etiologic factor will ever explain all cases. The hereditary influence, present in 40 per cent of our epileptic group, is a definite factor in many instances. Psychogenesis is offered by some as an explanation. Various chemical toxins, for example, strychnine, oxalic acid, or absinthe poisoning, and unknown or obscure toxemias, such as pregnancy, uremia, allergic sensitization, and so forth, are capable of producing convulsions. Endocrine glands, such as pituitary disorders, have been suspected, certain metabolic changes, such as hypoglycemia, disturbed calcium metabolism (spasmophilia), linked also with the endocrine dysfunctions, produce convulsions. Robinson, Brain and Kay[1] have recently found the blood cholesterol to be low in epileptics and to fall just prior to the onset of a convulsion, the fit taking place at the lowest point. No explanation of this abnormal metabolic phenomenon was given. Functional circulatory disturbances, blood-pressure changes as seen in fainting, heart block, and so forth, produce epileptiform spasm.

Hughes,[2] studying the effect of deficiency on vitamin A in mother's diet upon the brain of a fetus, reports a disorder of the nervous system, produced in young pigs by a diet free from vitamin A., consisting chiefly of ataxia, blindness, paralysis and convulsions. Dandy[3] has demonstrated on dogs that injury to the motor cortex lowers the threshold for the production of convulsions. Dogs so injured convulsed after one-third to one-seventh of the dose of absinthe necessary to produce convulsions in normal controls.

Ziegler[4] suggests from this work that idiopathic epilepsy is probably the result of injury to the brain which enables smaller insulting agents to induce convulsions. Injury probably occurs early in life and must be insidious and obscure to escape detection. In the light of recent work on vitamin deficiency the health of expectant mothers and the food of children should be given every consideration to prevent the type of injury to the brain that never can be repaired.

The multiplicity of factors producing convulsions illustrates the complexity of the problem of the pathogenesis of essential epilepsy and the reason for its obscureness. There are many factors as yet undiscovered.

Factors Promoting Epileptic Seizures. While it is generally believed by authorities that the essential epileptic is constitutionally predisposed to convulsive seizures (that is, the epileptic constitution), there are many factors that apparently precipitate seizures or aggravate seizures already present. A common observation in children is (in certain types) the occurrence of convulsions with each febrile upset. The finding of these factors such as Gordon's[5] careful study gives a lead in the treatment of the epileptic. In our group 26 cases (20 per cent) presented definite physical factors, such as definite focal infection or a history of convulsions following systemic infections or toxemias. Five cases fell into definite endocrine groups.

Relation of Infantile Spasms to Adult Epilepsy. In the considerable literature upon the subject, one finds but few careful statistical reports in comparison with normal controls. Opinions differ widely, according to the point of view. Many pediatricians, finding no relationship between ordinary infantile spasm and later more serious mental disturbance or convulsions, seemingly underestimate the significance of childhood spasms. Possibly the neurologist tends to overemphasize the significance.

Patrick and Levy[6] in a comparative study of 500 epileptics and a normal group of 751 infants concluded that convulsions (not epileptic) in infancy and childhood are evidence of the individual's tendency to later epilepsy. They found 20 per cent of their epileptic group had early convulsions and about 4 per cent in the control group. They believe their percentage was too low because of failure of patients or relatives to recall early spasms after the patient reached adult life. In general, they found the younger the epileptic the higher the incidence of infantile spasms in the history. The more likely forerunners of epilepsy are convulsions: (1) occurring before six or after eighteen months; (2) multiple; (3) severe (4) localized; (5) assigned to birth trauma, reflex causes or no cause; (6) with a family history of epilepsy or similar convulsions. The most significant are unilateral convulsions occurring after the fourth year, and generalized convulsions lasting over half an hour and followed by confusion or torpor for several hours. Especially benign appear to be "teething spasms" occurring between eleven and thirteen months.

Thom[7] found a much higher incidence of infantile convulsions in a study of 300 cases from an epileptic hospital; of these 50 per cent had convulsions prior to the fourth year. From study of another group with convulsions not diagnosed as epileptic, considered to be caused by acute infections, and so forth, before the fourth year, Thom concludes that the type of nervous system that reacts with convulsions in the presence of mild toxemia associated with gastrointestinal upsets is perhaps the type of nervous system that needs protection from environmental situations. Thus convulsions may perhaps be considered as the criterion of the stability or instability of the nervous system. His conclusions were based upon the fact that 56 per cent of these supposed nonepileptic infantile convulsions were malignant; either continued to death, typical epilepsy developed or the children were mentally deficient.

In our group 16 out of 124 (15 per cent) gave a history of infantile spasms. This percentage is undoubtedly too low. About half our cases were examined after twenty-one years of age. In many instances, accurate childhood history was not obtainable and parents were not present. Infantile convulsions should be considered seriously and parents so informed, since it seems likely that about 50 per cent will become epileptic or its equivalent.

The Relationship of Trauma to Epilepsy. The relationship of head trauma to the development of later epilepsy is exceedingly puzzling. In certain cases, evidence of a definite localized lesion can be found shortly after the trauma in the nature of hematoma from skull fracture or meningeal apoplexy. Here the convulsions usually are of Jacksonian type and early surgical intervention indicated. In a much larger group of cases the head trauma may be mild, yet serious convulsions follow that show no organic signs or pressure phenomena. In this group the accepted explanation by most authorities is that a previous epileptic predisposition has been excited into a frank epilepsy by the trauma. The more recent work of Dandy[3] showing lowered cortical threshold to convulsions after trauma of the motor cortex throws more light on the cause of these cases.

In our series there were 9 (4.5 per cent) that had convulsive seizures following head trauma. Four had localized findings of organic brain injury or hematoma formation. Two of these had had one or more decompression operations without relief of the spasms, since the residual brain lesion in the form of cicatrices is not benefited by surgery. Increased pressure is the safest criterion for decompression. In 2 cases the convulsions ceased after the acute pressure phase of the concussion subsided. The remaining 3 cases showed no organic signs; 2 of these had Jacksonian convulsions.

Petit Mal Attacks. A diagnosis of petit mal epilepsy is frequently missed, probably because of uncertainty of what constitutes a petit mal attack.

It is important to study carefully slight nervous tendencies in children. Sudden momentary stares, sudden feelings of fright, sudden tastes or smells, a causeless stop in play, laughing spells, sudden bobbing of the head or dropping to the floor, sudden sensations of unsteadiness or falling or transient dreamy spells may all be manifestations of epilepsy.

An example of an atypical petit mal type is as follows:

Case I.—Male, aged forty-four years, with a familial history of epilepsy, for fifteen years had been troubled with peculiar vertiginous-like attacks (a sudden sensation of falling or unsteadiness many times a day), causing him to avoid social contacts and embarrassing him greatly at work. Organically there was a rheumatic endocarditis present. Phenobarbital controlled the attacks almost completely. After two years' observation the patient died of cardiac decompensation. Necropsy showed a marked aortic stenosis.

Status Epilepticus. The development of convulsions in series is always a serious condition and in many of these serial types the convulsions come closer together with unconsciousness between the attacks, so-called status epilepticus. In our group, there were 4 cases (3 per cent) that developed status epilepticus. Two died, one in the first attack of status and one in the second. Two were

adults with onset after thirty-five years, one, a girl, aged seventeen years, had 140 Jacksonian convulsions in twenty-four hours. Exploration revealed no definite lesion of the motor cortex. The surgeon thought he could palpate a deep softened area.

Mental Disturbances in Epilepsy. A large percentage of essential epileptics develop some mental disturbance. These mental reactions vary from dullness, difficulty in thinking and memory impairment, behavior oddities, acute psychotic outbursts of extreme violence, to profound mental and emotional deterioration. Transitory psychotic states are common preceding, following, or replacing the seizures, so-called psychic equivalents. At times manic excitement or wild states of blind rage or furor during which the epileptic may attack any one. Upon regaining his normal mental status, the epileptic has no recollection of the acts.

We found 22 (18 per cent) of the 124 essential epileptics showed distinct mental reactions aside from the usual epileptic personality.

The following case illustrates one type of psychic equivalent:

CASE II.—Male, aged eight years, developed serial grand mal attacks at weekly intervals from three until seven years. Petit mal daily seizures then commenced. Each attack was followed by "angry, mean" spells that lasted several hours. Overactivity and motor restlessness progressed to the point of incontrollability. School progress was *nil*. The personality change was profound. The Binet-Simon test showed an I. Q. of 100, no organic factors were found. The general condition of the patient was worse while taking phenobarbital. Coincident with changing the intestinal flora by acidophilus preparations and a combination of bromids and belladonna his attacks ceased and normal behavior and school progress followed. For four years the patient has remained normal and free from seizures.

Migraine and Epilepsy. The relationship of migraine and epilepsy seems to be that of "first cousins." It has long been observed that migrainous heritage often produces epilepsy. The occurrence of both conditions in the same patient is not unusual. Phillips[8] classifies the cases in three types: (1) migraine occurring during early life, ceasing at menopause, and epilepsy developing later; (2) the group with epilepsy in earlier years and migrane later; (3) migraine and epileptic attacks alternating. He believes both conditions are due to cardiovascular disturbance and the relationship is coincidental. Flatau[9] found both conditions in 36 patients in a group of 500 epileptics.

In our group, definite migraine history in the family occurred in 12 (10 per cent). A double strain of migraine occurred once. While some of the records did not inquire specifically for both conditions in the same patient it was noted in instances; in each of these they were closely associated, usually alternating.

Jacksonian Convulsions. Focal or Jacksonian spasms occurred in 16 cases (13 per cent) of this series. Twelve cases of Jacksonian seizures were definitely from organic brain disease, usually focal

disease of the cortex, 3 cases followed birth hemorrhage, 3 followed vascular accidents (hemiplegias), 2 followed severe head trauma, 1 focal meningitis or encephalitis, and 3 cases from brain tumor. In four instances the Jacksonian spasms were essentially epileptic without demonstrable cause.

Wilson,[10] Collier, Mills and others have emphasized that Jacksonian convulsions are common in essential epilepsy. They go so far as to state that idiopathic epilepsy is the commonest variety of Jacksonian attacks. Wilson gives the warning, with which I agree, that Jacksonian cases should not be operated upon without definite evidence of intracranial disease. It is a much safer attitude, on the other hand, to consider all Jacksonian seizures as organic in nature until definitely proved otherwise and only by exclusion of all factors to call them essential epilepsy. A fair percentage of idiopathic epilepsies in the earliest seizures start as Jacksonian attacks and later become typical generalized convulsions. It is probable that each convulsion at its very onset is Jacksonian but quickly spreads bilaterally.

Hysterical Convulsions. Convulsive states are often one of the prominent motor symptoms of conversion hysteria. At times the differentiation from essential epilepsy is baffling. Certain cases seem to be a cross between the two conditions, thus leading to the hyphenated expression of hysteroid epilepsy. When this occurs I personally believe we have two conditions—an hysterical personality having true epilepsy. It is well known that organic diseases frequently have a psychoneurotic coloring.

The characteristic march of symptoms of sudden onset, always followed by unconsciousness in epilepsy, with usually some trauma to lips, tongue or body during the convulsions and with at times incontinence, usually labels the picture epileptic, not hysterical. In the hysteric, the convulsion is always psychogenetically determined, an exciting emotional cause usually present, without complete loss of consciousness but rather a fugue state of dissociation with amnesia following.

There were 11 cases (5 per cent) in our series of convulsive states of hysterical origin. In one unusual case during the tonic spasm hyperpnea developed to a degree that artificial tetany was produced from overalkalinization of the blood.

Narcolepsy. Strictly speaking, narcolepsy is not a convulsive state but its manifestations are epileptiform and by some it has been considered a form of epilepsy. These patients suffer from spells of dropping off to sleep which they are unable to control, and they frequently fall asleep under most inopportune conditions. In addition they suffer from sudden weakness of body musculature simulating paralysis during emotional disturbances such as laughter, anger, or excitement. Under emotional stress they suddenly lose all motor power and the legs give way, the patient usually falling

to the ground. This condition is called "lachschlag" by the Germans. Henneberg described it as cataleptic paralysis.

Spiller[11] and others have described this syndrome following encephalitis. In one of our patients the syndrome followed encephalitis. While narcolepsy is a relatively rare condition more cases than usual have been seen the last few years by all observers.

The following are illustrative cases of this condition:

CASE III.—Mr. J. M., aged forty-four years, a short time before our examination noticed attacks of sudden loss of motor power with some cramping of the muscles when endeavoring to carry out sudden movements while under emotional tension. This symptom had been noted particularly while hunting ducks, when ready to pull the trigger his body suddenly weakened, paresis of the arms developed, and he dropped the gun. Laughter or anger caused the entire body to weaken and at times to fall, the power of speech was lost during the spells. Narcolepsy had not developed.

A complete examination revealed no evidence of neurologic disease. This patient has noted a very definite improvement in the symptoms while taking continuous small doses of phenobarbital. When he ceased taking the drug the symptoms promptly returned.

CASE IV.—Mr. R. R. R., aged thirty-one years, received on top of the head of a severe blow from a 40-pound weight. No unconsciousness followed and work was resumed the following day. Within two weeks after the accident typical spells of falling to sleep began. At the same time spells of muscular collapse from emotional stimulation began, for example, while correcting the children, attempting to chase a dog, while laughing, or from fatigue he would fall to the ground. In addition, he had noted momentary semiconscious spells associated with twitching of the facial muscles, motor weakness and loss of power of speech. Excitement of attempted coitus produced semiconsciousness and muscular quivering with loss of power which prevented him from completing the sexual act. At times the patient had involuntary urination during the spells. The family physician described what seemed to be a generalized convulsion following one attack.

Prolonged observation has failed to reveal any evidence of organic disease. Deep Roentgen ray therapy over the hypothalamic region was tried without improvement.

Convulsions of Cardiovascular Origin. Riesman and Fitz Hugh[12] consider that epilepsia tarda includes a group of convulsive states having their onset after forty years of age. Cases without etiologic factors other than a periodic insufficiency of the cerebral circulation, they divided in three groups: (1) arteriosclerotic; (2) hypertensive; (3) mixed hypertensive and arteriosclerotic. They report 12 cases having the average age of onset thirty-six years. Because of underlying circulatory abnormality in all cases, they concluded that momentarily deranged cerebral circulation (cerebral anemia) was the exciting cause. Many died apoplectic deaths. They found convulsions in uremia to be rare and usually a terminal state.

In the cardiovascular group of our series I have listed 9 cases (7.2 per cent), 5 of which had onsets after forty-five years and

showed definite arteriosclerosis, with or without hypertension and myocardial degeneration or valvular defects. Two patients had associated mitral stenosis. One had an embolic apoplexy with residual Jacksonian convulsions, one syncopal attacks with cardiac insufficiency signs; both of these had their onset in the thirties. One case of meningeal apoplexy was followed by convulsions; one cortical vascular softening with right hemiplegia after head trauma was disclosed at operation.

Convulsions from Cerebrospinal Syphilis. Syphilis as a cause of convulsions has probably been overemphasized. Older textbooks classify convulsions beginning in middle life as usually from neurosyphilis. We do not find this to be true.

Cerebrospinal syphilis was found in 7 cases (3.5 per cent) of the entire group. Occasionally convulsions in children, the result of juvenile paresis, are overlooked and considered essential epilepsy. Two cases in this series were juvenile paretics. Two were adult paretics. Convulsions often give the first warning of approaching paresis. Three cases were meningovascular cerebral syphilis. Any convulsive disorder beginning in adult life should be closely observed for organic brain disease, and syphilis excluded by spinal-fluid studies.

Convulsions in Infantile Cerebral Palsy from Birth Hemorrhage. Mental retardation, hemiplegia and convulsions, one or all usually follow cerebral hemorrhage at birth. Children suffering from this unfortunate accident rarely survive without some sequelæ.

There were 8 (4 per cent) of this series of convulsive states that definitely were caused by birth hemorrhage. Five cases had a history of instrumental delivery, 2 prolonged difficult labors, 1 premature delivery. In 5 cases with hemiplegic findings the convulsions were unilateral Jacksonian type.

Convulsions in Brain Tumor and Abscess. These convulsions may be either an early irritative symptom, sometimes being present for years before other signs of tumor occur, or a late pressure manifestation. Convulsions in brain tumor are at times of localizing value, since they are common in tumor of the anterior chamber and unusual in posterior fossa tumor; more frequent in temporal lobe neoplasms than in occipital; easily caused by tumors growing near the motor area. Convulsions resulting from increased intracranial tension are of little localizing value.

There were 12 instances (6 per cent) in our series of convulsions from proved brain tumor or abscess. Two were brain abscesses, both in the temporal lobe. Of the tumors 6 were in the frontal or frontotemporal areas, 1 pituitary, 1 temporal lobe, 2 unlocalized. In 4 cases the convulsions (focal spasms of diagnostic value), were among the first symptoms, in 1 case preceding by nine years other definite symptoms of tumor. In 5 cases the convulsions were generalized, all showed high manometric pressure readings upon lumbar puncture and later proved to be tumor.

Examples of this type are as follows:

CASE V.—Male, aged thirty-five years, began having very severe attacks of generalized convulsions in series with no objective signs. Mental deterioration progressed after each series. Spinal puncture showed a pressure of 40 mm. of mercury after a convulsion, the fluid was slightly bloody. Decompression was done but death followed. Necropsy revealed a large soft glioma of the right frontal lobe.

CASE VI.—Male, aged forty-five years, had generalized convulsions for several years without localizing signs. The spinal-fluid pressure was 20 mm. of mercury. Aphasia and right hemiparesis developed. Operation disclosed a cystic glioma in the left motor zone. Marked functional improvement for two years followed by intermittent pressure signs developed, each time accompanied by convulsions.

Convulsions from Cerebral Inflammations. The occurrence of convulsions in acute meningitis is a common symptom, particularly in children, and in the more fulminating types is usually a grave sign. Residual convulsive states are frequent following a purulent meningitis in which external hydrocephalus or localized adhesive exudates remain, producing irritative lesions, lowering the nervous threshold of nervous irritability, and predisposing the individual to later epilepsy. In our series were 5 cases (2.5 per cent) of convulsions definitely traceable to encephalitic or meningitic processes.

Convulsions Occurring in Obscure Toxic or Organic Cases. In this group an accurate organic diagnosis was not possible in 11 cases (5.5 per cent). Four of these were probably vascular in origin of which one had a history of syphilis but negative serologic findings, and in all of which the onset was after forty years. Two cases suggested strongly brain tumor but were not proved. Two cases were from obscure cerebrospinal infections, one probably serous arachnoiditis, had a temporary cerebrospinal block with increased spinal pressure. The condition gradually subsided. The other resembled epidemic encephalitis. One child, aged four years, had a premature closure of the fontanelles with increased spinal pressure. Another patient had evidence of toxic convulsions from an obscure systemic infection. One patient had severe serial convulsions associated with hyperglycemia and mild nitrogen retention but without marked acidosis, apparently a toxic reaction the forerunner of diabetic coma.

The Management of Convulsive States. The first step in intelligent treatment of a convulsive state is obviously the finding of any etiologic factors and removing these. Only by exclusion of all organic and toxic causes are we justified in calling the seizures essential epilepsy. The necessity of an accurate diagnosis is the paramount issue. Convulsions beginning in middle life challenge us to very detailed examinations and should be considered organic until we can find no demonstrable cause. Those that are found to

be organic (symptomatic epilepsy) indicate special therapy. Intracranial pressure conditions require neurosurgical therapy. Those cases resulting from neurosyphilis, arteriosclerosis, cardiac insufficiency, and so forth, require treatment directed toward the underlying cause.

There is a large group of organic cases that cannot be handled in any other way than by symptomatic sedative treatment. These should be managed the same as essential epilepsy. Many of these residual convulsive-form lesions of the cortex respond well to drug therapy.

It is through prevention only, including better prenatal care to prevent toxemia of pregnancy and better obstetrics during parturition, that the incidence of birth hemorrhage convulsive states can be reduced. Spinal drainage until the fluid is clear should be done in these cases to prevent residual cortical defects. Acute cerebrospinal inflammations, where remediable, offer a field in preventive epilepsy. Meningococci meningitis too frequently has epileptiform sequelæ. Earlier and larger doses of serum given intracisternally quickly sterilize the subarachnoid system before adhesive exudates produce subarachnoidal blockage, and residual convulsions. In the infantile spasm group, greater care of these potential epileptics as to nutrition, rickets, and so forth, and prevention of physical and mental excesses during the growing period, offer hope in preventing adult epilepsy.

Hysteria. In the hysterical convulsive patient drugs should not be resorted to, but psychotherapeutic treatment in the form of reëducation through psychoanalysis, hypnotic suggestion, or other psychotherapeutic measures are indicated. An attack should be made upon the underlying hysterical constitution that is overreacting to some emotional conflict, showing itself as convulsions.

Post-trauma. The post-traumatic convulsive case is sometimes a difficult therapeutic problem, particularly in cases of Jacksonian spasm. In general, I believe that operative interference is of no avail unless evidence of intracranial pressure is present. We see a fair number of patients of this type having had one or more decompressions without relief. Symptomatic sedative treatment the same as for essential epilepsy is indicated. Operative interference soon after the onset of convulsions might be more favorable but in the delayed case surgery offers but little hope.

Narcolepsy. In this interesting syndrome because of inaccurate knowledge we are in etiologic darkness. Spiller in a personal communication stated he had found nothing to relieve the condition. In one of our cases the patient found definite relief while taking phenobarbital.

Symptomatic Treatment in Essential Epilepsy. Drug therapy resolves itself largely into sedative treatment to lower the threshold of cortical irritability. Practically every hypnotic has had a trial

in epilepsy. The drugs in present favor are the salts of bromin, and phenobarbital which is probably the drug of choice with the majority of authorities. Chloretone has a place in certain resistive cases and belladonna has a definite place, particularly when combined with bromids for petit mal types.

Bromids. Each patient must be individualized. As Clark stated, our principle should be to treat the epileptic, not his seizures. In certain cases, bromids very effectually control the seizures, in other cases, the addition of belladonna or the administration of bromids and phenobarbital is necessary. The usual rule has been to give sufficient bromid up to about 60 gr. a day to control the seizures. We use a colorimetric method to determine the bromid content of blood serum as recommended by Wuth.[13] The dosage can be regulated to prevent bromid intoxication.

Clark[14] states that in certain cases it is contraindicated to give a large enough dosage of sedative to control the attacks. A relative cure is frequently advisable because a chronic inhibition of attacks often causes a cumulative outcome and changes the character of the case from a benign to a malignant type. In any case the earlier vigorous treatment before the chronic state is established offers the best permanent outlook. Every patient must continue sedatives for years after the seizures cease before reducing the dosage.

Diet. Practically every form of diet has been advocated in epilepsy. The most recent diet therapy is the ketogenic, increasing the fat content and reducing carbohydrates until acidosis ensues. Maintaining acidosis is supposed to inhibit the convulsions; it also regulates normal bowel action. Careful trial of this method in children has not yielded the permanent results hoped for and drug therapy has been a necessary adjunct. I do not wish to imply that we see no merit in this treatment, but we believe the earlier reports are overenthusiastic. I can see no reason for extreme restrictions in diet. It is advisable to restrict indigestible articles, spices and stimulants. Excessive sweets and meats with children are to be avoided. Certain cases have seemed to be benefited by changing the intestinal flora by the use of acidophilus cultures and lactose.

Phenobarbital. This drug controls many grand mal cases completely. It is less effectual in the petit mal type. Dosage up to 3 gr. a day is permissible, above this usually producing intoxicating symptoms. Many cases require only $1\frac{1}{2}$ gr. each night.

Petit mal Types. Phenobarbital is often disappointing in this type. Many cases will respond when it is given with bromids. As stated before a combination of bromids with belladonna will relieve resistive cases. Where these measures fail, chloretone 2 gr. twice daily given with the other measures is helpful.

Status Epilepticus. Heroic measures are indicated in continuous serial convulsive seizures or a fatal result is likely to follow. Stren-

uous elimination is indicated, colonic flushing should be given at once. At times spinal drainage is helpful. Large doses of sedative are necessary Sodium phenobarbital intravenously is the most effective in doses up to 10 gr. for adults. Ether and chloroform anesthesia are of but temporary value and often dangerous. Cardiac support, increased fluid intake to overcome dehydration, and other symptomatic treatment may be indicated. Inhalation of amyl nitrite should be tried.

Migraine and Epilepsy. Phenobarbital frequently relieves the migrainous state as well as the convulsions. The double problem is often resistive to therapy. We must treat the individual constitutional problem as presented, correcting any fundamental defects found. One patient was symptomatically cured after removal of focal infection and the administration of endocrine therapy for definite hypopituitarism and thyroidism. The administration of cannabis indica along with phenobarbital aids many migraine cases. Allergic investigation may reveal protein sensitization, thus giving a clue to dietetic treatment.

Summary. In a clinical study of 200 convulsive states, 124 were essential epilepsies, and 76 other convulsive states with known etiology. Of the epileptics, a neuropathic heredity was present in 40 per cent; in 20 per cent physical factors were noted that facilitated the seizures. In 15 per cent there was a history of infantile spasms. In 18 per cent were definite abnormal mental reactions. Migraine occurred in 10 per cent in the family history.

Of the 200 cases 4.5 per cent followed head trauma. Jacksonian spasms occurred in 8 per cent; 12 of these cases were organic spasms and 4 were essential epilepsies. Decompressive operations have not improved the organic unilateral spasms in this series. The safest indications for neurosurgery are pressure signs.

Five per cent of the entire series had hysterical convulsions. Four cases of narcolepsy with "lachschlag" or cataplexy were found in the series. Five per cent of the cases had convulsions beginning in the arteriosclerotic age with signs of cardiac insufficiency sufficient to be considered etiologic. Cerebrospinal syphilis was responsible for 3.5 per cent of the cases. Birth hemorrhage with associated cerebral palsy was present in 4 per cent, tumor and brain abscess in 6 per cent. Attention is called to the convulsions that are an early symptom of brain tumor, at times present long before pressure signs and of diagnostic value. Residual convulsions from cerebral inflammatory conditions occurred in 2.5 per cent of cases. There were 5 per cent of cases classified as toxic and mixed organic types with obscure etiology.

Various methods of treatment are discussed with emphasis upon the proper management of essential epilepsy and with attention to the possible ways of preventing convulsive states.

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SPONTANEOUS INTRACRANIAL HEMORRHAGE FROM A VASCULAR TUMOR.

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When a spontaneous cerebral hemorrhage occurs in a young adult without traumatic injury, hypertension or syphilis, a cerebral vascular tumor should be considered as a probable cause of the hemorrhage.

Case Report. L. H., a young negro, aged twenty-six years, was brought in an unconscious condition to the John Sealy Hospital at 9 A.M., July 29, 1925. His wife said he had been in perfect health. The morning of his death he went to his work at a filling station. While sitting in a chair he suddenly complained of a severe pain in his abdomen. He coughed a few times, vomited a small amount of greenish-yellow material, fainted and fell out of the chair. He was sent to the hospital immediately.

Examination showed a well-nourished, unconscious young negro. The temperature was 97.8° F., the respirations shallow and 24 per minute. The pulses were full, equal, synchronous, and easily compressible, 68 per minute. The blood pressure was 124 systolic and 72 diastolic. There was a soft blowing systolic murmur localized at the mitral area. The chest and abdomen were normal. The pupils were contracted and reacted slightly to light. Nuchal rigidity was present. The reflexes of the upper extremities were normal, those of the abdomen and lower extremities were absent. The signs of Hoffman, Babinski and Oppenheim could not be elicited. There was no ankle clonus. Kernig's sign was positive. There was no response to any stimulus. A catheterized specimen of urine showed a trace of sugar and many red blood cells. The white count was 14,200, of which 91 per cent were polymorphonuclear cells, 6 per cent were lymphocytes, 2 per cent transitionals and 1 per cent mononuclears. A spinal puncture revealed an increased pressure and a uniformly bloody fluid. The Wassermann reaction was subsequently reported negative.

By 3.30 P.M. the pupils had become dilated, the temperature was 102° F., the pulse was 88 and the respirations 30 per minute. During the withdrawal of the specimen of spinal fluid the pulse became very rapid and breathing stopped. The needle was immediately withdrawn. Attempt to revive the patient failed.

Autopsy Report. The body was that of a well-developed, well-nourished young negro with no evidence of external abnormality or injury. Scalp and skull were apparently normal. Some extravascular fluid blood was present in the piaärachnoid, chiefly about the base of the brain and over the cerebellum.

The brain was sectioned by Virchow's method. All four ventricles contained blood: In the third and lateral ventricles partly clotted, in the right less blood than in the left. In the anterior wall of the anterior cornu of the left lateral ventricle was a hemorrhagic tumor mass extending medially into the genu of the corpus callosum. Mediolaterally this mass measured 25 mm. and anteroposteriorly 15 mm.; it extended into the brain substance 12 mm., the deepest part to within 5 mm. of the cortical gray matter of the left gyrus rectus (Fig. 1). The overlying cortical surface was apparently normal. Attached to the ventricular surface of the tumor area was a large bloodclot. Section showed the tumor somewhat spongy and trabeculated, with blood filling the meshes of the tissue. The chorioid plexus showed nothing unusual. No definite evidence of compression of the brain into the foramen magnum was found.

Microscopic examination of the tumor showed numerous intercommunicating blood channels (Fig. 2), varying from a 2-mm. diameter down to capillary size. Several of these vessels contained blood, and some were filled with it. All had rather thick, well-formed walls. A single layer of swollen endothelial cells lined the vessels and there were scattered fibers of smooth muscle in the walls, many of which, especially in their outer adventitial portion, showed thickening and hyaline degeneration. No evidence of calcareous infiltration was seen. Several blood spaces were found just beneath the ependyma and some were ruptured and the overlying ependyma torn.

The stroma between the vessels was made up of glial tissue showing hemorrhagic infiltration near the area of ruptured vessels and toward the periphery of the tumor infiltration with edematous fluid, enough in some areas to form definite collections which pushed the glial tissue aside. We found nothing abnormal in the brain cortex.

Small atheromatous areas were found in the aorta, and small scars in the apices of both lungs with an associated localized fibrous pleurisy. Microscopically, the myocardium showed segmentation and fragmentation. The other organs and tissues showed nothing unusual.

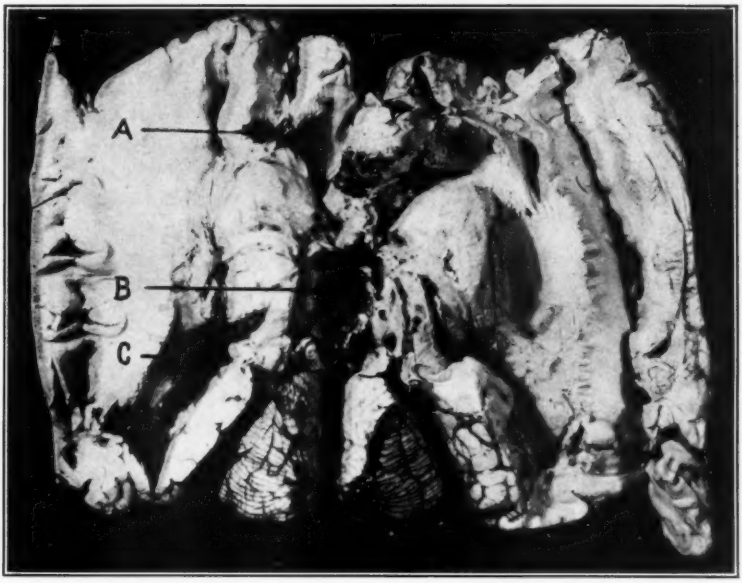

FIG. 1.—Hemorrhage into brain from vascular tumor: *A*, tumor area; *B*, hemorrhage into third ventricle; *C*, hemorrhage into left lateral ventricle.

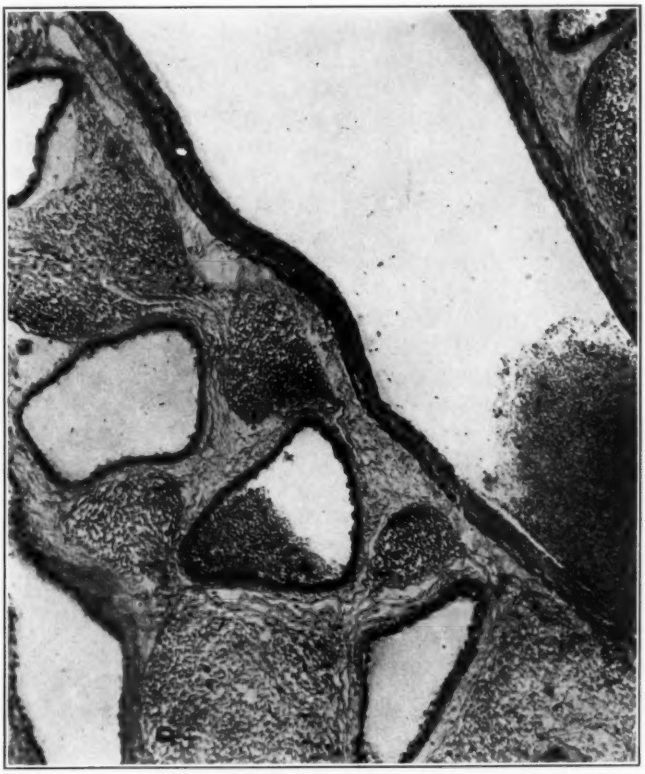

FIG. 2.—Photomicrograph of vascular tumor shown in Fig. 1.

Discussion. The etiology of cerebral vascular tumors is unsettled. Trauma may be a factor (Pineas,[1] Sachs[2]). A congenital origin is a widely accepted explanation (Ewing,[3] MacCallum[4]). In support of this view is the fact that multiple lesions of a similar vascular nature have been found in the skin, brain and liver, etc. (Jaffé',[5] Dandy[6]). Several cases are on record showing angioma of the brain associated with vascular nevi of the skin (Sachs,[2] Strominger,[7] Hebold[8]). Hemangioma of the retina (von Hippel's disease) may be also found in conjunction with angiomatous cysts of the cerebellum (Lindau,[9] Cushing and Bailey[10]). Cobb[11] has reported a case of hemangioma of the spinal cord associated with nevi of the skin at the same segmental level. These observations have led some authors to believe that there is a developmental association between the central and the peripheral lesion. Lindau[9] has shown that these angioblastic tumors of the nervous system are to be found associated with cysts of the kidneys, cystic pancreas, and tumors of the adrenal glands.

There are in general two main groups of these blood-vessel tumors. In the first group there are new and proliferating blood-vessels, while in the second group one finds dilatation and metamorphosis of preëxisting vessels (Virchow,[12] Adami[13]). Some cases in the first group have been reported that have apparently come from remnants of angioblastic tissue, while other cases of this group have apparently come from preëxisting more fully developed vessels (Ribbert,[14] Moise,[15] Schley[16]). In this first group, there are new growths made up essentially of blood and blood-vessel elements. These are spoken of as angiomas.

In the second group, one finds both those cases which have resulted from dilatation of preëxisting more fully developed vessels, somewhat after the histio-mechanical laws of Thoma,[17] and also those cases resulting from dilatation and metamorphosis of certain embryological vessels which had failed to undergo normal regression (Moise[15]). The conditions of this second group are spoken of as either telangiectases or hamartomas (Albrecht[18]).

Angiomas grow. Both clinically and pathologically there may be evidence of their growth (Ewing[3]). One is able to find, at least in some portion of these tumors, vessel walls that are poorly developed, and usually lined with two or more layers of endothelial cells. These tumors may be represented by numerous blind vascular spaces which are entirely separated from the general circulation and in such cases the blood found in these spaces is formed through the hemoblastic activity of the cells lining the spaces (Ribbert,[14] Luschka,[19] MacCurdy[20]). Other angiomas are connected up with the systemic circulation through either a vein, an artery, or both vein and artery.

In telangiectases or hamartomas one finds the vessels increased in size, but there is little evidence of new vessel formation. These

vessels or vascular networks, are usually lined with a single layer of endothelium and may show thickening and degenerative changes in their walls. In our opinion, the case reported here is a telangiectasia.

Hemorrhage from vascular abnormalities in the body has been mentioned in the literature, but has not been sufficiently emphasized in relation to cerebral vascular tumors. Epistaxis is frequently seen in hereditary hemorrhagic telangiectases of the nasal and buccal membranes (Osler,[21] Hanes,[22] Steiner[23]). Hemorrhage from hemangiomas may be a cause of paraplegia (Sargent,[24] and others). Wirgman[25] has reported a case of a young man, aged twenty years, with a fatal intracranial hemorrhage from an angioma in the cerebellar peduncle, who thirty minutes before death had been in a cheerful mood and apparently well. Müller[26] has described a case of a young man, aged seventeen years, who had been sick for five days with headache, became comatose and developed ocular palsy and cervical rigidity before death. The autopsy showed that death was due to a hemorrhage from an angioma situated in the region of the caudate nucleus. Latham[27] has reported a case of a man, aged forty-four years, who had suffered from headache for three weeks and was suddenly seized with epileptic fits and became unconscious. Five days later he died, and necropsy revealed a hemorrhage from a cavernous hemangioma at the juncture of the right frontal lobe and precentral gyrus. Dandy[6] has reported a case in a man aged 30, who died suddenly while on the way to the operating room for relief of brain tumor symptoms. Postmortem examination showed a large hemorrhage into the occipital and temporal lobes, coming from a small angioma in the region of the angular gyrus.

Summary and Conclusion. A case of fatal intracranial hemorrhage from a cerebral vascular telangiectasia in a young man is reported, with autopsy findings, and brief review and discussion of the literature. A vascular tumor should be borne in mind as a possible source of intracranial hemorrhage, when such hemorrhage occurs in a previously healthy young adult.

NOTE.—For a more extensive consideration of the symptomatology, pathology and treatment the reader is referred to the writings of Sachs, Lindau, Dandy, Cushing and Bailey.

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CEREBRAL HEMORRHAGE FROM VENOUS AND CAPILLARY STASIS.*

A Report of Five Cases with Autopsy.

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These 5 cases are reported together because all showed hemorrhage into the brain substance from congested veins and capillaries.

* Read by title at the meeting of the Association of American Physicians, May, 1929.

Etiologically the cases are not similar: of the 3 with thrombosis of the dural sinuses and pial veins 1 (Case I) followed pneumonia and phlebitis; another (Case II) resulted from purulent meningitis; the third (Case III) had an unsuspected pericarditis. The other 2 are patients who were asphyxiated, one by illuminating gas (Case IV) and the other at birth because of respiratory failure of the mother. In these 2 there is no question of infectious thrombosis of the veins or dural sinuses, but great stasis and congestion of the cranial veins is known to occur during asphyxia. This has been observed experimentally by Forbes and Wolff[1,2] and is a common clinical observation. From the clinical standpoint, the cases are similar in that all died after a prolonged period of unconsciousness, during which 4 of the patients had convulsions, while the fifth (Case IV) had muscular twitchings.

Interest in the vascular lesions of the brain has centered upon the arterial side of the circulation. Ever since the epoch-making work of Charcot and Bouchard the question of arterial cerebral hemorrhage has been intelligently investigated. Hemorrhage from the veins and capillaries of the brain, however, has received comparatively little attention. Judging from the small amount that has been written on this aspect of cerebral hemorrhage, such lesions might be considered either rare or of little importance. Lesions like those herein described are often designated as "hemorrhagic encephalitis." The observations on these 5 cases indicate that encephalitis, if present, acts on the bloodvessels merely by thrombosis. The hemorrhage apparently results from a mechanical obstruction to the venous circulation with its increased venous pressure plus anoxemia.

Case Reports. CASE I.—(N–27–73.) A WOMAN, AGED FORTY-SIX YEARS WITH A REMARKABLE FAMILY HISTORY OF PHLEBITIS. AFTER BRONCHOPNEUMONIA AN EXTENSIVE PHLEBITIS IN THE LEGS, ABDOMEN AND FINALLY IN THE VEINS OF THE DURA AND BRAIN. CONVULSIONS AND DEATH IN COMA. AUTOPSY: TREMENDOUS THROMBOSIS OF ILIAC VEINS UP TO VENA CAVA AND OF VENOUS SINUSES OF DURA. CONGESTION, HEMORRHAGE AND SOFTENING OF NUMEROUS AREAS IN THE BRAIN.

Clinical History: Family History. It is interesting to note in connection with the phlebitis reported below, that during three generations of the family, there have been 7 cases of very extensive phlebitis, most of which have proved fatal.

Past History. The patient was a woman, aged forty-six years, the mother of six children. Eighteen months previously, she fell from a horse and suffered a concussion of the brain. This was not followed by any apparent ill effects.

Present Illness. Following a month of fatigue while tending a daughter with pneumonia, the patient developed a fever of 105° F. On May 15, a physical examination showed cyanosis, pain over the upper right chest, definite râles at the apex and questionable consolidation of the right apex and base. The white blood count was 13,000; pulse, 100; blood pressure, 110 systolic and 80 diastolic; blood culture, negative. On May 19, the

condition was much the same; at this time a sputum culture showed Type IV pneumococci. A diagnosis of bronchopneumonia was made. On May 24 the pneumonia had spread to the left lung. On June 1 the patient complained of pain in her right thigh and said that she was going to have phlebitis; two days later phlebitis was present. Two weeks later phlebitis developed also in the left leg. On June 23, the bronchopneumonia was still present with phlebitis in both legs. At this time convulsive movements set in; these started in the left side of the mouth and then spread to the left forearm, hand and fingers. These unilateral convulsions came at intervals of two or three hours, later they became more frequent, and after about eighteen hours there was one convulsion on the right side and one general convulsion. A blood culture at this time was negative. On June 23, the patient lapsed into unconsciousness; this condition was maintained until her death on June 28.

Summary of Autopsy Report.* *Lungs.* In the trachea, and bronchi of both lungs there is found a large quantity of purulent material. Through the branches of the pulmonary arteries there is extensive thrombosis, some of the branches apparently being completely occluded. There are extensive adhesions of both lungs to chest wall and diaphragm. The chief pathology of the lungs is in brief: bronchopneumonia, with chronic bronchitis, peribronchitis and bronchiectasis; alveolar emphysema; chronic fibrous pleuritis; pulmonary thrombosis.

Spleen. Acute splenic tumor.

Liver. Shows small, pale areas scattered through the liver, presumably caused by obliteration of the sinusoids by greatly swollen liver cells filled with glycogen vacuoles, such as are often found in individuals where death is due to cerebral traumatism.

Heart, gall bladder, gastrointestinal tract, kidneys: all essentially normal.

Dissection of the Veins of the Abdomen and Legs. Thrombophlebitis of both femoral veins, internal and external iliac veins and their tributaries. Thrombosis of the common iliac veins and inferior vena cava. Thrombosis of the ovarian veins and the veins of the vesical, vaginal and uterine plexuses.

Middle Ears. Normal.

Sphenoidal Sinuses. Both filled with a turbid, thick, mucoid material.

Pituitary Gland. Normal.

Calvarium. Careful examination (in view of the history of concussion) showed no evidence whatever of any traumatic injury to the bone.

Sinuses of the Dura. The posterior part of the superior longitudinal sinus is filled with a firm red clot which is continued through this toward and into the jugular foramina. From the midportion centrally in both lateral sinuses the clot is only partially occluding and is adherent to the external walls of the sinus. The cavernous sinuses on both sides are apparently free from clot.

Brain. Examination of the Fresh Brain. There is marked flattening of the convolutions on both sides. There is very marked discoloration of the surface of the brain on the right side involving the anterior and posterior central gyri and the posterior portion of the superior parietal lobe. On the left side, this discoloration involves the anterior and posterior central gyri only, but at this point the consistency of the brain is soft, almost fluctuant and an incision across the fissure of Rolando reveals a fairly large cavity, anterior to this sulcus, filled with a soft red brain substance and bloodclot. The central portions of both the precentral and postcentral gyri present opaque grayish areas thickly studded with minute hemorrhagic areas. On the right side, the same description applies both to motor gyri and to the

* These first eleven paragraphs are a summary of an extensive report kindly given us by Prof. S. B. Wolbach, under the file No. H-27-890 at the Harvard Medical School.

region posteriorly situated. No further incisions were made. The base of the brain appears to be normal. Cerebellum, pons, and medulla are apparently normal externally. The arteries and veins at the base of the brain are normal in appearance. The brain was fixed in 10 per cent formalin and given to the Department of Neuropathology for further study.

Examination of the Hardened Brain. On frontal section through the frontal lobes about 4.5 cm. from the frontal poles, there is an oval hemorrhagic area, 1 by 0.5 cm. just lateral to the base of the left superior frontal sulcus, and 1 cm. from the surface. It involves chiefly the gray matter and shows many pin-point hemorrhages. There is a second darkened area in the left hemisphere at the same level; this is 1 by 1.5 cm. and lies in the white matter directly under the left superior frontal gyrus, and about 0.5 cm. from the midline. As already noted, when examining the fresh brain, the surface over these lesions shows dark, hardened, thrombosed vessels with perivascular extravasation of blood. The areas of softening, discoloration and petechial hemorrhage under the surface appear to be associated with the thrombosed vessels at the surface.

A second section (Fig. 1) cut 0.5 cm. posteriorly to the first section, passing through the anterior tip of the lateral ventricles and the genu of the corpus callosum, shows a continuation and enlargement of these two lesions. The more lateral area, now 2 by 1.5 cm. involves all of the gray matter at the base of the left superior frontal sulcus. Median to this lies the second area, 1.5 by 1 cm. and about 1 cm. from the midline. Although it lies 0.5 cm. from the surface, it is connected with the thrombosed vessels at the surface by darkened extravasated blood extending down into a small sulcus. The right side at this level is quite clear except for a very few pin-point hemorrhages in the white matter.

A third section cut more posteriorly passes through the anterior perforated substance, the temporal lobes and the anterior portion of the corpus striatum. On the left side between the superior and middle frontal convolutions, there is a wedged-shaped area 1.5 cm. long and 0.5 cm. wide of opaque jellylike, material which obliterates the fissure between the convolutious. In the left inferior frontal convolution, there is a grayish-green area 1 cm. below the surface and 1.5 by 1 cm. in size, the periphery of which is studded with minute pin-point hemorrhages of brownish color, and the center of which is necrotic and largely liquefied. This is later seen to be the anterior end of a large softening which extends backward and downward in the left hemisphere. The right side is normal except for a slight discoloration and a few pin-point hemorrhages in the superior frontal convolution. The superior sagittal sinus is filled with a dark-red clot.

The fourth section is made through the postcentral gyrus, and passes through the midthalamus, tail of the caudate nucleus, and the cerebral peduncles. This shows the superior sagittal sinus filled with thrombus, the center of which is gray, becoming progressively browner as the periphery is approached. On the left side, there is a cavity communicating with the subdural space which gapes widely and extends deeply into the white matter for 5 cm. This opening (incision) was made at the time of the autopsy. About 1 cm. medianward from the opening, there is another greenish area with many punctate hemorrhages, in size 1.5 by 0.5 cm. About 1.5 cm. medianward to this, with its apex downward, there is a blunt triangle about 2 cm. in width involving the superior portion of the paracentral gyri; this has similar color changes and many pin-point hemorrhages. In the right postcentral gyrus about 3 cm. from the midline, there is an area of greenish-yellow tissue 2.5 by 2.5 cm. surrounded by many pin-point hemorrhages. These areas of discoloration and hemorrhage appear to be associated with thrombosed vessels on the surface, as do the areas seen in sections already described.

A fifth section (Fig. 2) passes through the parietal lobes, splenium of the corpus callosum, cerebellum and pons. The left side shows the cavity wider but not so deep. (In the accompanying figure, the cavity appears greater than it really is due to the incision made at autopsy.) The walls of the cavity are covered with grayish-green necrotic material. The medial wall consists of a reddish-stained area extending from the external surface about 1.5 cm. deep and 1.5 cm. from the midline. The lateral wall of the cavity extends from the aperture downward into the middle of the white matter underlying the inferior parietal convolution, and thence medially to within 2 cm. of the midline. The superior sagittal sinus is completely filled with thrombus which is grayish and very firm. The right hemisphere shows a triangular greenish-yellow area in the white matter, this area extends upward toward the cortex where there appear innumerable pin-point hemorrhages, the whole area being about 1 by 2.5 cm.

The next section, through the middle of the precuneus and cerebellum, shows the superior sagittal sinus still thrombosed completely: the inferior sagittal sinus is not only patent but empty. On the left is a round area 2.5 cm. from the midline just subjacent to the gray matter, greenish in color and 1.5 by 1.5 cm. in size. On the right side, similarly placed is a larger softened and hemorrhagic area which extends to the surface. Just beneath it, but separate is another spot about the size of a pea. All three present the characteristic pin-point hemorrhages described above.

A cut through the occipital lobes presents much the same picture, the lesions on both sides extending backward into the cuneate gyri.

The cerebellum and brain stem present no apparent gross abnormality.

Summary. The brain presents two large areas of softening (see Fig. 2*a* for diagrammatic location), of which that in the left hemisphere is the larger, beginning about 1.75 cm. below the cortex of the operculum of the inferior frontal convolution and extending backward toward the occiput to become, in the paracentral region, a cavity of approximately 20 cc. volume; this ruptured and opened on to the surface of the brain at autopsy. As the lesion proceeds backward the cavity reaches within 1.5 cm. of the body of the left lateral ventricle. The posterior aspect of the cavity ends just posterior to the ramus lateralis of the sulcus cinguli, whence the softening continues as a narrow area beneath the superior parietal lobe to the middle of the precuneus. On the right side, a roughly spindle-shaped softening begins 5 cm. from the frontal pole in the superior frontal convolution and proceeds backward; its largest portion is in the paracentral region; posteriorly it tapers off to end in the precuneus. Several small hemorrhagic areas are directly contiguous with the two main lesions.

Microscopic Examination of the Brain. Sections for microscopic study were taken from the superior sagittal sinus, and from two different parts of the left superior frontal gyrus. These were stained: *a*, with hematoxylin and eosin; *b*, with Spielmeyer's myelin sheath stain.

The section through the superior sagittal sinus shows a thrombosed vessel. There is nothing particularly unusual, the thrombosis being the usual picture in which organization has taken place around the periphery and is working in toward the center, the center being somewhat canalized. The tissue around the vessel is filled with blood clot which is speckled with dark pigment much of which has been ingested by phagocytic cells.

The sections through the cortex show many pial vessels thrombosed, some showing organized thrombi. Where these sections have cut across a sulcus, a thrombosed vein may be seen extending into the depths of the sulcus. These, too, are surrounded with dark pigment, much of which has been ingested by phagocytic cells. The brain substance itself shows many areas of hemorrhage. In certain areas the hemorrhage is present most abundantly in the gray matter; in other places the white matter is chiefly involved;

some of the hemorrhagic areas extend into both white and gray matter. These areas are of various sizes; they are congested and edematous and are made up of clusters of small capillary extravasations. These are mostly circular and many have the appearance of a ring around a central cluster of large mononuclear cells, many of which have ingested red blood cells or pigment. Occasionally a bloodvessel may be seen within one of these areas of hemorrhage, but generally the hemorrhage is so dense that all underlying structure is obscured. Many of the vessels which are seen in the substance of the brain are thrombosed, this is true not only of the larger vessels, but also of the smaller branches.

Fig. 3 shows various points of interest that seem to explain the mechanism of the petechial hemorrhages. Beyond the limits of the photograph (to the left and upward) there is a thrombosed vessel, completely occluded and partially organized on the surface in the pia. This can be followed as it runs along the sulcus deeply into the brain substance where it shows across the upper part of Fig. 3. The sulcus is filled with a clot. In the gray matter near the sulcus (*S*) there is a little hemorrhage, but considerable edema. At a deeper level there is abundant hemorrhage which involves chiefly the gray matter bordering the sulcus, but which extends slightly into the white matter. Many of the hemorrhages in the proximity of the sulcus appear as streaks, this is because there has been much diapedesis from these small vessels; their walls appear to be much damaged and many of the vessels are traceable only as streaks of free red blood cells. Further out from the sulcus, the areas of hemorrhage are more circular and considerably larger. The hemorrhage is limited mostly to the lower side of the sulcus, above there is merely congestion of the capillaries and larger vessels, such as is seen in the area where gray matter merges into white (*x*). This is between the mass of linear and confluent extravasations in the gray matter and the more spherical hemorrhages in the white matter (*W*).

In a final note on the autopsy Professor Wolbach says: "In spite of the failure to obtain growth from the cultures and to demonstrate evidence in the histologic study, the extensive thrombosis of veins and cerebral sinuses must have been initiated by an infectious process localized in the vein in probably more than one situation. I have seen similar conditions in typhoid fever and in typhus.

"The lungs give positive evidence of a long continued bronchitis, persisting from a bronchopneumonia which, because of the peribronchial and interstitial pneumonitis, was probably streptococcal, possibly influenzal (Bacillus influenzæ) in origin. The lungs would seem to have been the most probable source of blood-stream invasion leading to the thrombosis inasmuch as thrombosis of pulmonary veins (not found in the present case) is not infrequent in the present type of lung infection.

"There is no histologic evidence of peculiarity of the veins in this case; on the other hand, there is abundant evidence of normal sequences taking place in the processes of repair, in organization, canalization and establishment of collateral routes as seen in the tissues surrounding the veins selected for study.

"The cause of death was cerebral softening due to the extensive blocking of venous routes from the brain."

CASE II.—(N–21–239.) GIRL, AGED TWO AND A QUARTER YEARS, WITH OTITIS AND MENINGITIS FOR THREE WEEKS, CONVULSIONS THREE DAYS, COMA AND DEATH. AUTOPSY: THROMBOSIS OF PIAL VEINS AND CONGESTION, HEMORRHAGE, SOFTENING AND ABSCESS IN UNDERLYING BRAIN TISSUE.

Clinical History. A girl, aged two and a quarter years, was admitted to the Children's Hospital on December 6, 1921. The illness was of three

weeks' duration, beginning with a stiff neck and poor appetite. About a week later, there had been vomiting and a discharge from the right ear. She became increasingly ill, later developing a slight cough. Three days before death she began to have irregular jerking and twitching of the mouth, arms and legs.

Physical examination at this time showed a prostrated and sick-looking child, who noticed nothing that was going on. There was a thick mucoid purulent discharge from the right ear. Moist râles were heard throughout the chest. The neck was held stiffly and movement caused pain. There were frequent spasms which involved the right side of the face, but in which the motor division of the fifth nerve did not take part. There were general spasms of the body which were marked by an extensor rigidity of the left arm and leg, and a flexor rigidity of the right arm and leg. The corneal reflex on the right was absent. The eye grounds were normal. The blood Wassermann was positive; red blood cells, 2,900,000; white blood cells, 12,700; hemoglobin, 50 per cent. Lumbar puncture showed a clear fluid under slightly increased pressure with 30 white cells per c.mm. and 18 red cells. Just before death the spinal fluid became opalescent, the pressure increased, the white cell count was then 320 per c.mm.

Autopsy Findings. The pleural cavities, pericardial cavity, heart, spleen, gastrointestinal tract, pancreas, kidneys, adrenal, aorta and genitalia were all essentially normal. The lungs showed bronchitis, peribronchitis, areas of bronchopneumonia and a pulmonary infarct in the left lower lobe. The liver showed a small amount of central necrosis and fatty infiltration.

Gross examination of the brain showed thrombosis of the sinuses and cortical veins. The superior longitudinal sinus is engorged, bulging, and very firm to the touch. On opening it, it is seen to be completely thrombosed. Both lateral sinuses are prominent, and, with the inferior petrosal sinus, are found to contain thrombi. The jugular veins are not thrombosed. Many pial veins are thrombosed, they are bulging, reddish black in color and firm in consistency (Fig. 4).

Extending over the superior aspect of the parietal lobes, there is a purulent exudate. This is thickest along the course of the veins, but is found also lying in the sulci and to a less extent spread over the cortex. The exudate is limited in area to the superior aspect of the parietal lobes, and the frontal and occipital poles. The base of the brain is free from exudate.

There are numerous small punctate reddish-black hemorrhagic areas on the surface of the cortex in the posterior half of both frontal lobes superiorly, and practically over the whole of the superior surface of both parietal lobes. The left lateral hemisphere is larger than the right and gives a definite fluctuating sensation to palpation. The cranial nerves, cerebral arteries, and entire base of the brain are normal except for the presence of a pressure cone on the under surface of the cerebellum.

On making frontal sections through the brain, hardened in formalin, from before backward the following points are noticed. In the anterior portion of the frontal lobes there is blood in the sulci and numerous fine dark-red punctate hemorrhages throughout the gray and white matter; one ecchymotic patch about 2 cm. in diameter is confined almost entirely to the gray matter of the middle frontal gyrus. On sectioning through the right middle frontal gyrus there is found a cavitation containing blood and pus. This measures vertically 2 cm. and from 4 to 8 cm. transversely (Fig. 5). It is surrounded by punctate hemorrhages of varying size and the white matter adjoining it is of a dirty yellow color; on the left side the sulci are engorged with blood; the gray matter adjacent to them is of a reddish color, bordered by punctate hemorrhages in the white and gray matter. The next section, through the fissure of Rolando, reveals a practically normal condition in the right frontal lobe, while on the left there are extensive punctate and also

fairly large hemorrhages in both white and gray matter. Extending obliquely into the insula from the midportion of the corona radiata there is an irregularly shaped necrotic, ragged abscess measuring 2.5 by 1.5 by 1 cm. in the central portion of the left parietal lobe. Directly opposite to the posterior horn of this cavity, there is an extensive brownish discoloration of the globus pallidus, claustrum, external capsule, caudate nucleus, and superior fibers of the internal capsule. A section directly through the splenium of the corpus callosum and cutting the cerebellum shows discrete and confluent punctate hemorrhages in the gray and white matter of the parietal lobes for a distance of about 5 cm. lateral to the longitudinal fissure, somewhat more extensive on the left side. Finally, a section through the occipital lobe shows the same condition to a very slight degree, and also a small amount of blood in some of the sulci.

The brain stem and cerebellum are essentially normal.

Microscopic Examination of the Brain. Sections through the cortex show three main lesions: (1) thrombosis of the cortical vessels (Fig. 6); not only are the surface vessels thrombosed, but also thrombi may be found in the smaller branches which extend down into the brain substance. The large surface thromboses are definitely organized; some of the smaller, deep thrombi are likewise organized. The veins that are not occluded are greatly congested and many show extravasation of red cells.

2. There is a purulent exudate over the surface; this infiltrates the pia arachnoid; it consists mostly of polymorphonuclear leukocytes, but there are also some mononuclears present. Leukocytes may also be found in abundance in the bloodvessels.

3. There are circumscribed areas of hemorrhage of variable size throughout the white and the gray matter. Scattered through these are scavenger cells and numerous polymorphonuclear leukocytes most of which are in a poor state of preservation. In these areas, there is marked congestion and edema. The normal nerve cells have completely disappeared; the glia cells are separated by vacuolated, lacelike, edematous spaces (Fig. 7). The more solid areas which stand out as islands in the softer edematous tissue show a striking congestion and capillary injection. All the capillaries in such areas are engorged with red blood cells and hence stand out conspicuously from the surrounding tissue. Occasionally one of these is found to terminate in a cluster of red blood cells which were apparently showered into the surrounding tissue by the ruptured capillary.

CASE III.—(N–28–25.) GIRL AGED FOURTEEN MONTHS WITH SUDDEN ONSET OF VOMITING AND TWO DAYS LATER UNILATERAL CONVULSIONS. DEATH ON FOURTH DAY. AUTOPSY: PERICARDITIS, ARACHNOID HEMORRHAGE, THROMBOSIS OF SUPERIOR SAGITTAL SINUS, CONGESTION, EDEMA AND HEMORRHAGE OF SMALL AREAS OF UNDERLYING BRAIN.

Clinical History. A child, aged fourteen months, was seen at home in status epilepticus. The past history was unimportant except for a short attack of fever four and a half months previously with vomiting.

The present illness began with a recurrence of the vomiting; milk and lime water were given, but the vomiting continued. The temperature at this time was 99.4° F. Two days later, physical examination showed a well-developed child with no abnormal physical signs. The neck was not stiff. On the fourth day, after the vomiting had somewhat abated, convulsions began. These involved the right side, including face, arm and leg. At this time the child became unconscious. Examination of the right retina showed three hemorrhages. The rectal temperature was now 102° F. The child was taken to the hospital about twelve hours before she died. Lumbar puncture was performed. Thirty cubic centimeters 50 per cent

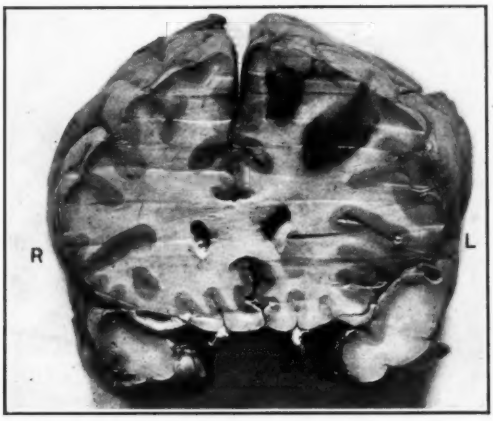

FIG. 1.—Section through anterior tip of lateral ventricles and genu of corpus callosum showing in the left hemisphere two areas of multiple minute hemorrhage with discoloration and softening at their centers. The upper lesion is seen to connect with the surface of the brain by a sulcus which contains a thrombosed vein.

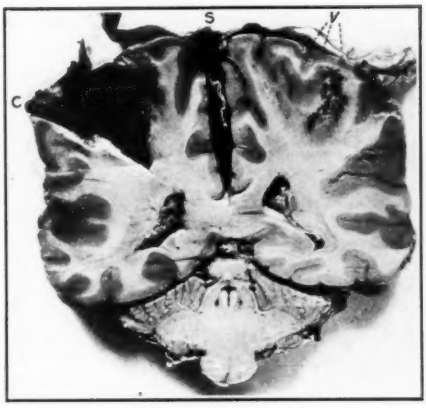

FIG. 2.—Frontal section through splenium of corpus callosum, cerebellum and pons. The large area of softening and hemorrhage (left) is exaggerated by a cut (*C*) made at autopsy to promote hardening. The sinus (*S*) is seen to be filled with thrombus. At "V" are indicated three small thrombosed veins in the pia; a typical area of petechial hemorrhage with slight softening underlies these.

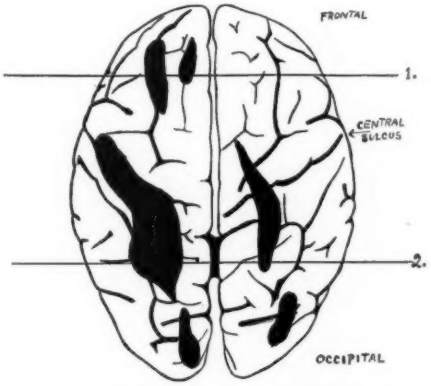

FIG. 2*a*.—Diagram showing location of main lesions in black. These lie deep in the brain as is seen from Figs. 1 and 2. The levels of the sections from which figures were made are indicated on the chart at "1" and "2."

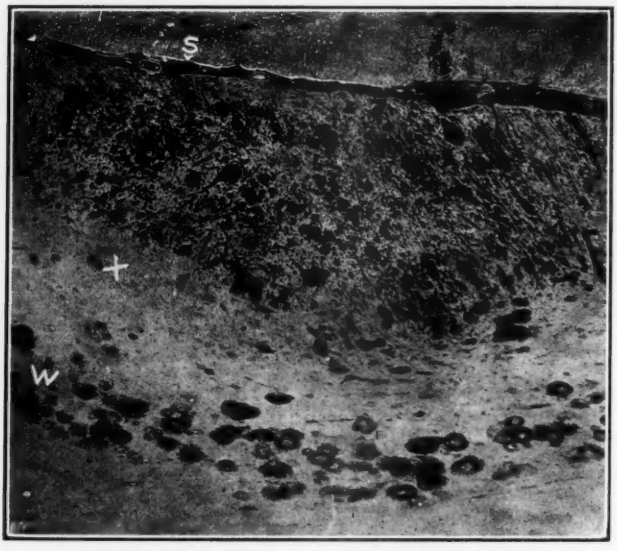

FIG. 3.—Low-power photomicrograph of area of multiple petechial hemorrhage near a thrombosed vein in a deep sulcus. For description see text.

Fig. 4

Fig. 5

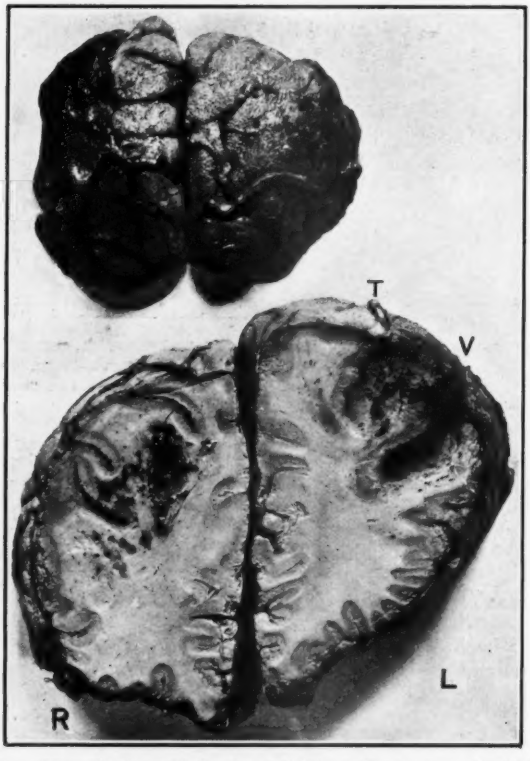

FIG. 4.—(Case II.) Surface of the frontal lobes showing meningitis and prominent thrombosed veins.

FIG. 5.—(Case II.) Frontal section through frontal lobes. In the white matter of the right hemisphere is an abscess cavity surrounded by punctate hemorrhages. In the left hemisphere is a hemorrhagic and softened area subjacent to thrombosed veins on the surface. One of these (V) is surrounded by frank hemorrhage, another (T) is seen distended with clot on the surface and filled with organized clot on section.

FIG. 6.—(Case II.) (Low-power photomicrograph.) Two large pial veins are seen filled with thrombus and surrounded by exudate. Along the sulcus beneath are many smaller veins greatly congested, some show the extravasation which makes the petechial hemorrhages.

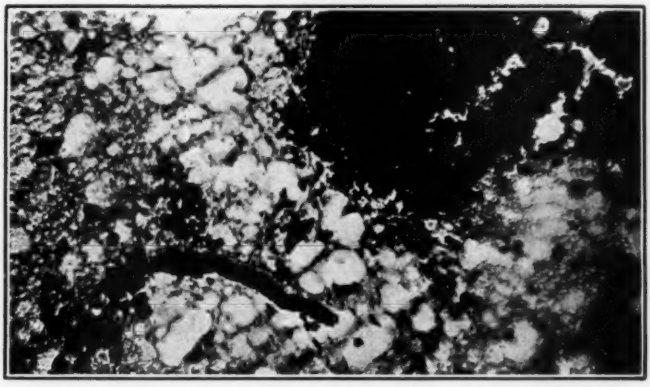

FIG. 7.—(Case II.) (High-power photomicrograph.) In the upper right-hand corner is a hemorrhage; the tissue about this is softened and edematous. In the lower left is seen a distended capillary the left end of which has ruptured and caused a minute hemorrhage.

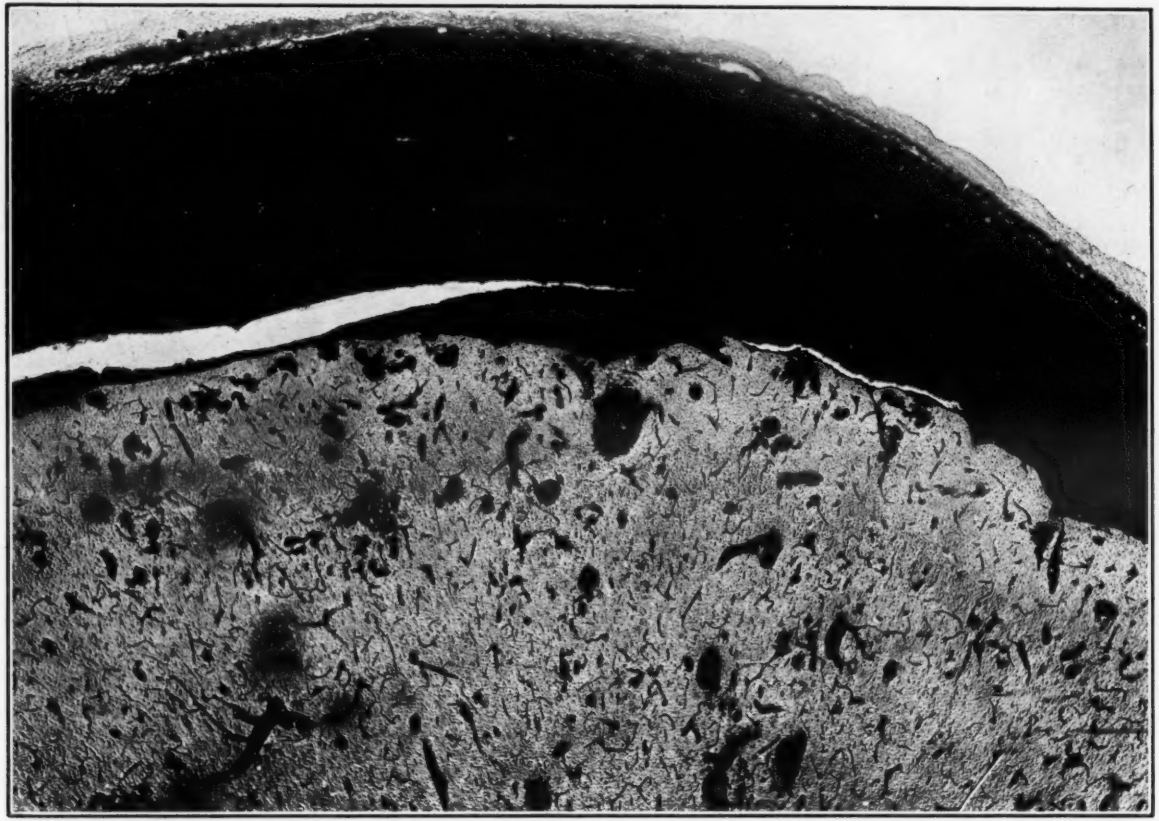

FIG. 8.—(Case III.) Subarachnoid hemorrhage (*H*) lifting up the outer arachnoid membrane (*A*) and compressing the pial veins. In the cortex (*C*) all the vessels are greatly congested. Many of them have extravasated red cells about them; a few have ruptured and caused punctate hemorrhages.

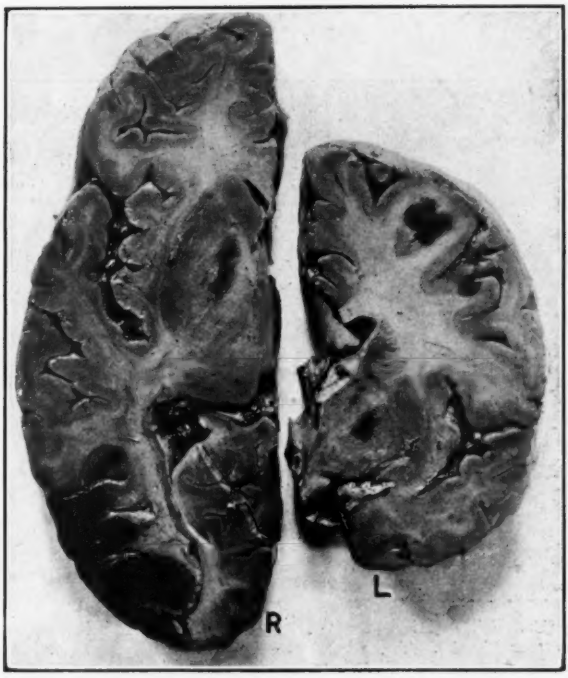

FIG. 9.—(Case IV.) The horizontal section of the right hemisphere (*R*) shows an area of softening with discoloration and hemorrhage in the globus pallidus of the lenticular nucleus. In the cortex of the occipital lobe is an extensive hemorrhagic area, the periphery of this is made up of discrete minute hemorrhages, which in the center are confluent and softened. A vertical frontal section of the left hemisphere (*L*) shows one of the many small hemorrhagic areas in the cortex; there is also a small lesion in the globus pallidus similar to that in the right hemisphere.

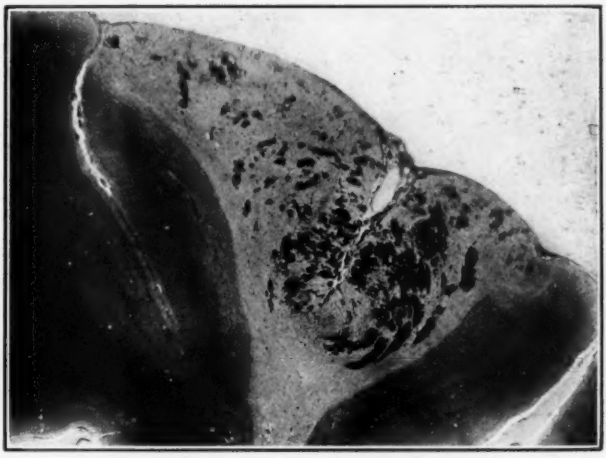

FIG. 10.—(Case IV.) (Low-power photomicrograph.) Small group of petechial hemorrhages in cortex, grouped about one sulcus as if dependent upon one venous outlet. The lesion is most marked in the gray matter but extends into the less vascular white. There is little blood in the arachnoid space.

veins. In the cortex (*C*) all the vessels are greatly congested. Many of them have extravasated red cells about them; a few have ruptured and caused punctate hemorrhages.

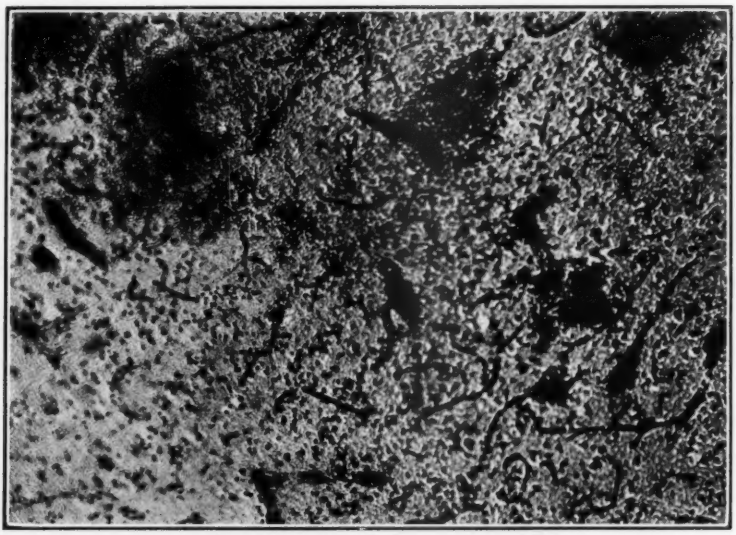

FIG. 11.—(Case IV.) (High-power photomicrograph.) This is an enlargement of a small area from Fig. 10. There is great congestion of the bloodvessels with occasional rupture and hemorrhage. The lower left-hand part is white matter, the upper and right-hand two-thirds is gray; the greater vascular supply and more numerous hemorrhages in the gray matter are obvious.

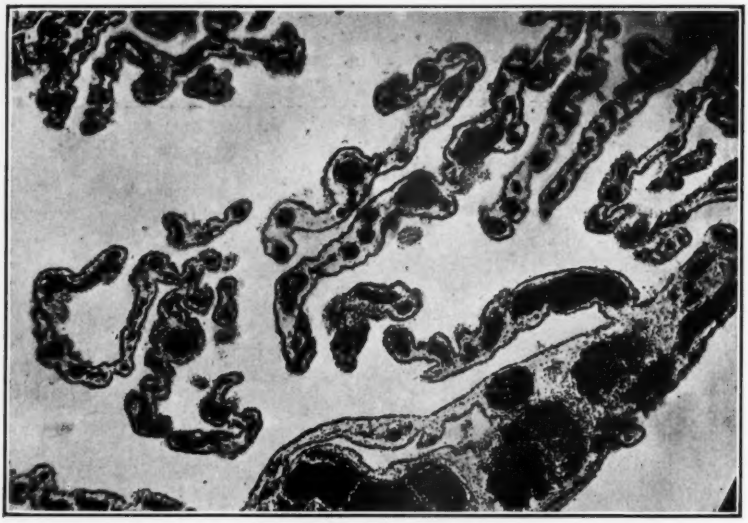

FIG. 12.—(Case V.) (Low-power photomicrograph.) Congestion of the choroid plexus with some extravasation of red cells into the interstitial spaces. (Morgan stain.)

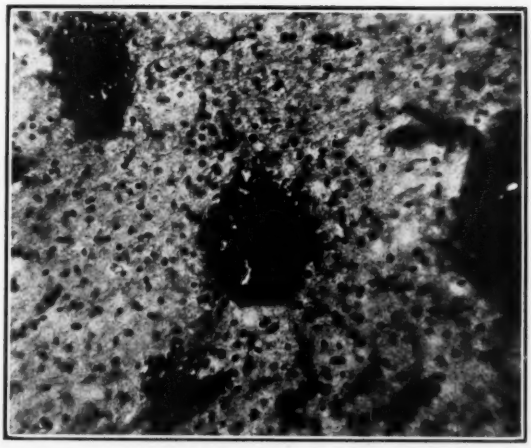

FIG. 13.—(Case V.) (High-power photomicrograph.) Section through the medulla showing great congestion of veins and capillaries with slight infiltration of the red cells out into the surrounding tissue. (Morgan stain.)

glucose were injected intravenously. The temperature rose to 108° F. As the child was dying a ventricular puncture was performed.

Summary of Autopsy Report. The only significant lesion found in the general viscera was an organized pericarditis, for which there was no apparent cause. The lungs showed a slight congestion; the liver slight congestion and some fatty infiltration; the cortex of the adrenal was unusually narrow. The important changes were found in the brain.

Brain: Gross Findings. The dura was normal except for a single needle puncture on the right side of the fontanel. There was no free blood in the subdural space. The pia-arachnoid space on the left was distended with a recent, diffuse extravasation of blood. The superior sagittal sinus, straight sinus, and portions of the lateral sinuses were distended with clotted blood which was deep maroon in color, firm, friable, suggesting antemortem thrombosis. The large superficial cerebral veins were distended like firm cords over the cerebral hemispheres on both sides. The capillaries were but little injected. The brain was normal in size and contour, and felt homogeneously soft. The convolutions on the right side were slightly flattened and the sulci slightly obliterated. The convolutions on the left were completely obscured by the blood in the arachnoid space. The vessels at the base were normal.

After twenty-four-hours' fixation in formalin, it was noted that the brain had a distinctly different appearance to that of the fresh state described above. The convolutions on the left were now apparent as very much enlarged and flattened gyri with obliterated sulci. The whole of the left hemisphere was now soft and semifluctuant as compared with the right which was of normal consistency.

On making frontal sections of the hardened brain, the extent and character of the hemorrhage is seen to better advantage. As noted at autopsy, it is limited to the left side. The sections show further that it is limited to the frontal and parietal lobes. The surface of the left temporal lobe is somewhat discolored, but shows no true hemorrhage. The hemorrhage consists of a very dark, hardened clot, which lies in the arachnoid, raising this membrane up from its normal position on the surface of the cortex. The clot extends into the sulci, widening them and compressing the cortex. The gray matter in these regions is discolored, giving a dark reddish-gray appearance through which may be seen small pin-point hemorrhages. The clot has distended the lateral fissure (of Sylvius) with extensive hemorrhage around the insula; it distends all the sulci of the parietal lobe; it extends into the longitudinal fissure and thence into the sulcus cinguli.

In a more anterior section, which cuts through the genu of the corpus callosum, and through the anterior portion of the basal ganglia the extent and character of the hemorrhage is much the same: limited to the frontal lobe, extending into the sulci, and compressing the discolored gray matter. In addition, this section shows a large clot widely distending the central sulcus and encroaching extensively into the cortex of the inferior portion of the precentral gyrus. Here the gray matter not only shows the discoloration noticed elsewhere, but is damaged by petechial hemorrhages and softening.

There is another distinct lesion running through the more anterior portion of the corpus callosum on the left. This dark oval area is due to the ventricular puncture performed at the time of death.

Brain: Microscopic Examination. A section cut from the superior sagittal sinus, shows bloodvessels congested and filled with blood cells. There is partial thrombosis. Throughout the thrombi of the sinuses there are numerous mononuclear leukocytes containing phagocyted hemosiderin. In the dura itself there are a few foci of polymorphonuclear leukocytes.

Microscopic sections were made from the superior frontal gyrus, the

conspicuous feature of these sections are, first, of course, the subarachnoid hemorrhage, and second, a great congestion of all the bloodvessels in the cortex beneath (Fig. 8). The bloodclot at the surface shows no unusual features. It is very dense, extends into the sulci wherever possible, and all through it are numerous phagocytic cells which have taken up hemosiderin.

All the vessels of the gray matter, the larger branches and the small capillaries, are distended with blood, making the vessels stand out very prominently. Occasionally a vessel may be found which has begun to thrombose. There are diffuse perivascular hemorrhages; around the larger vessels they may be quite large, and around the capillaries they may be minute, consisting of a cluster of blood cells which appear to have escaped from a ruptured capillary. As in the large surface hemorrhage, there may be found in these smaller hemorrhages numerous phagocytic cells containing ingested pigment.

There is also edema in the gray matter.

The lesion in the corpus callosum, which was noticed in the gross sections, shows an area in which the myelinated fibers of the corpus callosum have undergone degeneration. The area has rather a homogeneous pinkish aspect. Throughout it are numerous scavenger cells which have phagocyted particles of the degenerated myelin. It is rather striking that there should be phagocytic reaction in view of the fact that the injury was made at the time of death.

CASE IV.—(N–28–18.) WOMAN, AGED EIGHTY-SIX YEARS, ASPHYXIATED WITH ILLUMINATING GAS, ARTERIOSCLEROSIS AND PARALYSIS OF ARM, UNCONSCIOUS, LIVED THREE DAYS. AUTOPSY: CALCIFICATION OF ARTERIES, MARKED ACUTE HYPEREMIA OF ALL ORGANS, NUMEROUS HEMORRHAGES ON PIAL SURFACE OF BRAIN AS WELL AS IN THE GRAY AND WHITE MATTER OF THE CORTEX. SMALL AREA OF SOFTENING AND HEMORRHAGE IN EACH GLOBUS PALLIDUS. CORTICAL HEMORRHAGES MADE UP OF NUMEROUS SMALL PUNCTATE EXTRAVASATIONS COALESCING. CHRONIC DEGENERATIVE CHANGES IN BASAL GANGLIA.

Clinical History. The patient, white woman, aged eighty-six years, was found in a room filled with illuminating gas. On entrance to the Boston City Hospital, there was a strong odor of gas on her breath; the respiration was deep and labored, all accessory muscles being brought into use. The rate was rapid. There was a flaccid paralysis of the right face and a spastic paralysis of both arms, more marked in the left than the right. Myoclonic twitching of the arms and legs occurred frequently. All the reflexes were hyperactive. The lungs were emphysematous with many râles. Heart not enlarged to percussion. Rate, 120; blood pressure, 111 systolic and 75 diastolic. There was slight pitting edema of the legs. Diagnosis was made of gas inhalation, senility, arteriosclerosis, myocardial insufficiency, and cerebral vascular accident with paralysis. The patient was given oxygen inhalation for twenty minutes with no effect on the breathing. Caffeine, adrenalin, and intravenous digalen strengthened and slowed the pulse, and caused less labored breathing. The patient did not regain consciousness from the time she was found until her death three days later.

Summary of Autopsy Findings by Professor Leary: Heart. The mitral orifice is slightly calcified. Slight hyperplasia of the left ventricle. The right heart is considerably dilated. The coronaries show calcification.

Lungs. Acute passive hyperemia.

Liver. Acute passive hyperemia.

Gall Bladder. Cholelithiasis.

Genitalia. General senility with periovaritis, perisalpingitis and bilateral hydrosalpinx.

Kidneys. Chronic progressive vascular nephritis. There was a universal acute passive hyperemia, and considerable arteriosclerosis, although this was not greater than might be expected in an individual of this age.

Brain. Examined in the Department of Neuropathology, after hardening in 10 per cent formalin. The meninges are quite normal; they strip off freely from all parts of the brain except over areas of hemorrhage in the cortex. The size of the brain appears to be normal. The convolutions are not flattened. All of the vessels appear more prominent and dilated than usual, and are quite pink in color. The middle cerebral arteries show regions of opacity with beginning calcification.

The conspicuous feature is the presence of several areas of hemorrhagic softening (Fig. 9) which on palpation in the fresh state showed some fluctuation. These areas do not project above the surface of the cortex; there is no arachnoid hemorrhage, the hemorrhage is limited entirely to the substance of the cortex itself. One of these areas lies 3.5 cm. from the anterior pole of the right hemisphere and 2.5 cm. from the midline; this is oval in shape, 3.5 cm. in width, and 5 cm. in length. There is a similar area over the occipital pole of the right hemisphere; this is 5.5 cm. in width.

On sectioning the right hemisphere, the necrotic area in the frontal region is found to extend to a depth of 1.5 cm. It is pyramidal in shape, with the base at the surface. The large necrotic area at the occipital pole extends into the white matter to a depth of 2.5 cm. from the surface of the cortex. Throughout the cut surfaces, minute areas of perivascular hemorrhage and necrosis can be seen. The largest of these, about 1 cm. long is situated in the basal ganglia and has largely destroyed the globus pallidus.

In the left hemisphere, similar areas of softening are found. Over the anterior pole there are small rather diffuse areas. A somewhat larger area involves a small region both in the postcentral and precentral gyri. The largest area is in the occipital lobe and is about 3 by 4.5 cm. The sulci in this hemisphere appear wider than those in the right hemisphere, especially in the anterior pole.

On sectioning the left hemisphere, minute areas of perivascular hemorrhage appear as they did in the right hemisphere. A large area extends through the gray matter of the cortex from the region of the precentral gyrus to the large necrotic area in the occipital lobe. Again there is an area of necrosis in the globus pallidus (Fig. 9).

Except for minute areas of perivascular hemorrhage and injection of the vessels, the midbrain, cerebellum and hind brain show no gross lesions.

Microscopic Examination of the Brain. Turning to a study of the microscopic preparations of the brain lesions, a very interesting picture is found in a section through the comparatively slight hemorrhage, mentioned above, found in the globus pallidus. Here there is apparently a two-fold lesion: an old chronic vascular disease which undoubtedly antedates the carbon monoxide poisoning; and the more direct results of the hemorrhage and the reaction to it. There is marked thickening and hardening of the vessels. They stand out as darkly-staining rings, which on closer inspection are seen to be composed of hyaline droplets in the walls of the vessels. This condition of the vessels is limited to the globus pallidus, which is also the limit of the area of hemorrhage in this region. In the globus pallidus there are no normal nerve cells; the glia cells are abundant, but many of these too have undergone partial necrosis. The hemorrhagic process in this area is less clear than in sections of the cortex to be described below, but here, too, there are found capillaries congested and distended with blood cells; occasionally one may be found that has just ruptured. There is a pronounced reaction to this hemorrhage; especially prominent are the great number of scavenger cells, some of which have taken up pigment from the red cells. Also there are to be found numerous "mulberry bodies" in the

pallidum and many corpora amylacea beneath the pia. Cloudy bluish areas of degeneration are seen which may be regarded as "mucoid degeneration"[3] an early stage of these same "mulberry bodies" or corpora amylacea.

A section made from one of the hemorrhages in the cortex of the occipital lobe is illustrated in the accompanying photograph (Fig. 10). Here the vascular disease of the vessels (which was seen to be a striking feature of the condition in the globus pallidus) is not present. The area of hemorrhage is sharply marked off. It is definitely pyramidal in shape and involves mostly the gray matter. The normal nerve cells have completely disappeared, while glia cells are abundant. The most prominent feature is the marked congestion (Fig. 11). All the capillaries are packed with red cells. Quite frequently small capillaries, or sometimes somewhat larger vessels, may be seen to have ruptured. Some may be found where the rupture is very small and only a few blood cells have escaped, while others are seen around which there is a greater collection of red cells. The reaction to the hemorrhage is less marked than in the globus pallidus. There are scavenger cells, some with phagocyted particles and pigment as before, but they are not numerous. The whole picture is that of acute congestion with diapedesis of red cells, small extravasations, and small hemorrhages from capillaries and veins.

CASE V.—(N-29-1.) INFANT ONE DAY OLD. PROLONGED ASPHYXIA, CONVULSIONS AND DEATH. AUTOPSY: YELLOW SPINAL FLUID, EXTREME CONGESTION OF ALL OF THE VESSELS OF THE BRAIN, SCATTERED PETECHIAL HEMORRHAGES THROUGHOUT AND IN CHOROID PLEXUS AND ARACHNOID SPACE. ALSO HEMORRHAGE IN MYOCARDIUM, LUNGS, LIVER, KIDNEYS, ADRENALS AND PLEURÆ.

Clinical History. The patient, a male baby, one day old, was delivered by Cesarean section, spinal anesthesia having been used. During the course of the delivery the mother stopped breathing; artificial respiration was administered for two hours. At the end of this time the baby was delivered; he was blue and cyanotic with marked difficulty in breathing, and he had several convulsions. The following day he was brought to the Children's Hospital. Physical examination showed irregular and shallow respirations with periods of apnea. Coarse, crepitant râles were heard at the bases of both lungs. The skin was of a dusky color, indicating poor circulation. The baby was in the hospital for two hours before death. During this time there was one convulsion. Caffeine in small doses was given for the respiratory difficulty.

A lumbar puncture, performed postmortem, showed a yellow fluid with many red blood cells and few white blood cells.

Summary of Autopsy. *Cavities of the Body.* The peritoneal cavity shows no hemorrhages of the peritoneal surfaces. The visceral pleura and the visceral pericardium both show numerous hemorrhages, mostly along the course of the bloodvessels.

Heart. Gross examination shows numerous petechial hemorrhages into the myocardium and papillary muscles. Microscopic examination shows greatly congested bloodvessels and capillaries, especially marked in small areas of hemorrhage in the epicardium. Quite an extensive hemorrhage is found in the pericardium most marked about the larger branches of the coronary vessels.

Lungs. There is atelectasis. Congestion, with multiple hemorrhages extend well into the deep portions of the lung tissue. There is no gross picture of pneumonia, but the microscopic sections show acute bronchopneumonia.

Spleen. The only abnormality found is an extreme congestion.

Gastrointestinal Tract. There is no definite hemorrhage but considerable congestion in the mucosa and submucosa.

Liver. There is considerable hemorrhage into the liver substance. Microscopically there is seen some hematopoiesis; extreme congestion and a marked periportal infiltration of inflammatory cells.

Kidney. The pyramids are extremely congested. On microscopic examination, there are found to be multiple hemorrhages in the medulla with comparatively few such hemorrhages into the cortex.

Adrenal. The right adrenal shows a fairly large hemorrhage in the medulla. In the left adrenal there are several small hemorrhages chiefly in the medulla. The cortex is fairly normal.

Gross Examination of the Brain. The membranes—falx, tentorium and meninges—are intact and show no evidence of inflammatory reaction. There is a marked congestion of the vessels over the surface of the cortex and a few scattered, small areas of dark red, perivascular hemorrhage, measuring 0.5 to 1 cm. in diameter. There are a few small areas of subarachnoid hemorrhage over the frontal lobes. At the base of the brain there is similar congestion of the vessels; one small, dark-red hemorrhagic area appears at the cerebellopontine angle.

After hardening the brain in formalin for several weeks, it still is very soft and fluctuant with no ability to hold its shape. On making frontal sections, it is seen that the congestion, noticed upon the surface view, extends throughout the brain substance so that the injected bloodvessels stand out quite clearly. The choroid plexuses are congested. A section through the pons, peduncles and dentate nuclei, seem to show even more congestion, if possible, than the rest of the brain. A section through the medulla shows similar congestion.

Microscopic Examination of the Brain. Sections were made through several areas of the brain and cord, and were stained with hematoxylin and eosin, Morgan's hematoxylin[4] and cresyl violet.

A section through one of the subarachnoid hemorrhages of the frontal lobe shows sparse scatterings of red blood cells which have not as yet clotted, lying in the arachnoid space. Such hemorrhage is limited to rather a small area. In the brain substance below the surface there is marked congestion.

A section from the ventricular wall near the choroid plexus of the lateral ventricle shows extreme congestion of all the bloodvessels and capillaries. There are several small perivascular hemorrhages and in a few locations there are areas of more diffuse hemorrhage with a general scattering of red blood cells through the tissue.

A section through the corpus striatum on the left shows similar congestion and perivascular hemorrhage. There appears to be some edema; the perivascular and perineuronal spaces are swollen. The nerve cells of the basal ganglia are somewhat swollen and have undergone slight chromatolysis. The choroid plexus also shows extreme congestion. All the bloodvessels are packed with cells and there is extravasation of corpuscles into the interstitial spaces. This is of interest in relation to the yellow spinal fluid (Fig. 12).

A section passing through the hind brain and cerebellum, at the level of the pons and dentate nuclei, shows a degree of congestion even more marked than in those sections already described. Here all the bloodvessels and capillaries stand out as if an elaborate injection experiment had been performed. The richer blood supply of the gray matter shows in contrast to less vascular white matter. There is little hemorrhage at this level, but occasional perivascular hemorrhages may be found which are apt to occur around the larger vessels as well as around the capillaries (Fig. 13). The nerve cells are somewhat swollen and show chromatolysis.

A section through the upper spinal cord shows the same congestion, and here again the greater blood supply to the gray matter is apparent. There is slight edema, swelling of the nerve cells, and dilatation of the perivascular and perineuronal spaces. There is no hemorrhage seen in the cord.

Examination of sections stained with hematoxylin and eosin from various parts of the brain brings out the point that the veins are always much more congested than the arteries. This is especially apparent where, as in the meninges, a vein may be found lying near an artery. It is then observed that the artery although usually filled with blood is not at all distended whereas the vein usually is conspicuously distended. Numerous arteries were found which were almost empty with near-by veins extremely congested.

Discussion. The first case is one of hemorrhage associated with extensive sinus thrombosis. Here the thrombosis is most complete in the superior longitudinal sinus, extending into the lateral sinuses. Numerous cases of injuries resulting in thrombosis of the lateral sinuses have been reported, but interest in them seems to have been mainly from the point of view of otology. Injury to the superior longitudinal sinus is described much less frequently in the literature. In 1859 there was reported a case of traumatic obstruction of this sinus, the injury giving rise to no apparent continued intracranial disturbance.[5] This case was buried in the literature until the World War, when interest was aroused by the abundant cases of traumatic injury primary in the cerebral veins. In war wounds such injuries were quite common. Holmes and Sargent[6] present a review of 70 cases of war injuries involving the superior longitudinal sinus. The characteristic gross pathology which these cases showed was thrombosis of the superior longitudinal sinus with the cortical veins swollen, firm, and often thrombosed. The superior parts of the hemispheres drained by these veins were swollen and edematous, with the convolutions flattened out by pressure. Minute hemorrhages were present, and in a few cases, hemorrhagic softening with surrounding punctiform hemorrhages. The microscopic pathology of the affected areas showed edema and minute hemorrhages with many perivascular extravasations. If the lesions, as revealed by autopsy, are kept in mind, it is easy, as the authors point out, to understand the clinical symptoms. The motor symptoms were first those of the cortical areas nearest the median fissure and hence nearest the seat of the lesion, the superior longitudinal sinus.

Bagley[7] reviews 4 cases of extensive extravasation from the venous system of Galen. The clinical signs are: a sharp early rise in the temperature, pulse and respiration; a muscle disturbance chiefly of a spastic nature; blood in the spinal fluid; decreased intracranial pressure. Pathologically these cases show hemorrhagic extravasations varying in size from small microscopic lesions to large venous infarcts with extensive softening. Further light has recently been thrown on this subject by Doyle[8] who reports 4 cases of thrombosis of the superior longitudinal sinus.

Turning to the Case I reported here, one sees only slight similarity to the clinical features as reported by Holmes and Sargent and by Doyle. The pathologic picture bears a greater resemblance. The venous return of the blood is shut off as in the cases of sinus thrombosis reported by Holmes and Sargent and by Doyle; this is similar also to the cases of injury to the vein of Galen as reported by Bagley. Resulting from the venous stasis, there is a damming back of blood into the smaller vessels and a consequent hemorrhagic extravasation and softening. The probable cause of the softening and hemorrhage is discussed further in connection with the case of illuminating gas poisoning described below (Case IV).

The second case is quite similar to the first in several features. Here too there is sinus thrombosis, but this time following cerebral meningitis. The history presents a story of a discharging ear which is presumably the site from which the infection spread to the meninges of the brain, causing the meningitis, thrombosis of the pial veins with stasis of the deeper veins, anoxemia, softening and abscess formation. In this instance, the thrombosis is quite definitely the result of meningeal infection. The numerous punctate hemorrhages lead to a preliminary diagnosis of "hemorrhagic encephalitis." It would seem more logical to describe the hemorrhage and softening as direct results of the block in the venous return due to venous thrombosis.

The third case shows an extensive arachnoid hemorrhage. As is shown by the history, there is no trauma, no apparent cause for the condition. But a pericarditis was found at autopsy and thrombosis of the cerebral sinuses and veins. This arachnoid hemorrhage appears to have arisen from a venous disturbance. The clinical picture is analogous to that reported by Neal,[12] there was vomiting, fever and convulsions. The neck was not stiff, due, perhaps, to the fact that the hemorrhage was fairly well limited to the frontal and parietal lobes, leaving the base clear. As in the case reported by Neal, microscopic study shows pronounced edema, marked congestion of all the bloodvessels, particularly the capillaries, and numerous small petechial hemorrhages in the cortex. Of especial interest here, moreover, is the fact that the surface vessels are thrombosed which, along with the picture of edema and venous stasis, allows for an explanation of the hemorrhage on the same basis as in those cases already discussed: an occlusion of the venous return, a damming back of the venous blood and a consequent rupture of vessels, mostly in the brain substance, but of one at least in the subarachnoid space. It might be argued that the arachnoid hemorrhage occurred first and by pressure on the cortex obstructed the veins, thus causing cortical stasis. The pressure of extravasated venous blood would not seem to be high enough to do this; moreover thrombi were found in the pial veins. It seems more likely that the mechanism which caused the venous and capillary hemorrhages in the cortex, caused a vein in the arachnoid space to rupture.

In the past the discussion of subarachnoid hemorrhage[9, 10, 11, 12] centered almost entirely upon the arteries. No doubt many such hemorrhages are of arterial origin—certainly the most spectacular ones are. But is it not possible also to look for the etiology on the venous side?

The fourth case is rather an unusual case of poisoning from illuminating gas—unusual, not in the type of the lesion, but in its extent. The pathologic features of this type of cerebral injury are quite familiar. From a study of 63 cases of death from carbon monoxide poisoning, McNalley[13] describes a characteristic pathology: symmetrical punctate hemorrhage and softening in the globus pallidus, and less frequently similar lesions in the cortex. The microscopic pathology had been less often reported than the gross, but when described, it is the usual degenerative changes of nerve cells, demyelinization, glial reactions, and the presence of gitter cells.[14] In addition, there is, in the cases of acute poisoning, hyperemia, so that all the vessels, not only the veins, but also the arteries and the smallest capillaries are congested and dilated.[15] Thus it is seen that the pathology, gross and microscopic, of the case reported here presents the usual features but with unusually extensive areas of hemorrhage and softening in the cortex.

Ruge[16] gives a review of the various explanations of softenings. These include the following viewpoints: that the lesion is the direct result of carbon monoxide on the bloodvessel walls resulting in fatty degeneration and rupture of the vessels; that the softenings result from thrombi; that the lesion is primary in the nervous tissue with a secondary vascular lesion. Ruge himself maintains that there is both a primary necrosis of the nerve cells and a vasomotor paralysis with subsequent stasis, which results in ischemia and nutritional disturbances. Ferraro and Morrison[14] found that in the acute stages of poisoning there was a swelling of the endothelium of the bloodvessels: they suggest that this swelling may reduce the lumen of the bloodvessel and so tend to cause nutritional changes of the nervous tissue. It is improbable that the lesion is primarily the effect of the gas poisoning upon the bloodvessels with hemorrhage and consequent softening, for similar lesions are found in Case V where asphyxia alone caused extreme congestion and numerous minute hemorrhages. Landis[17] had shown in his beautiful experiments that anoxemia causes increased permeability of the capillary walls. Anoxemia also causes degeneration of brain tissue, as in the ordinary arterial infarct. In the cases here presented the anoxemia comes from venous stasis and blood stagnation, not from ischemia, but the result on the brain tissue is the same: softening and hemorrhage. What causes the great dilatation of the veins in carbon monoxide poisoning is not known, but it has been observed in the pia to occur regularly and quickly after inhalation of CO_1. Thus, although there is no gross block in the veins, as in the cases of

thrombosis described above, the slowed bloodflow and methemoglobinemia may cause enough anoxemia to make hemorrhages occur from the congested capillaries.

Summary. Five cases are presented which at autopsy showed hemorrhage into the parenchyma of the brain. In all of these the extravasation came from the veins and capillaries; there is no evidence that blood escaped from arteries. The mechanical factor common to all these cases is venous stasis, the common chemical factor is asphyxia. It is pointed out that widespread lesions can be caused by these two factors, the unit lesion being a petechial extravasation, but large lesions are formed by coalescence, and frank venous hemorrhage may be found. Such cases are more common than is generally supposed.

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REVIEWS.

MECHANO-THERAPY. By MARY REES MULLINER, M.D., Pp. 265; 57 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $2.75.

THE first part of this textbook deals with the procedures, the physiological effects and the technique of massage and movements. One chapter is devoted to the relation of the patient and operator and another one to planning the prescription of exercise for treatment. In the second part of the book the author discusses the treatment of various pathologic conditions by the means of massage and exercises.

The volume being on the whole well written, although rather elementary, should not be without value to nonmedical students and practitioners of mechanotherapy. J. N.

FIBROADENOMATOSIS CYSTICA MAMMÆ AND ITS RELATION TO OTHER PATHOLOGICAL CONDITIONS IN THE MAMMA, ESPECIALLY CANCER. By CARL SEMB, formerly First Assistant in the Pathologico-anatomical Institute of the University Hospital, Oslo, Sweden. Pp. 484; 37 illustrations. Oslo: Nationaltykkeriet, 1928.

THE material studied was derived from 144 cases of fibroadenomatosis in women, and 14 in men, while for comparison the normal mammary glands from 32 cadavers were used.

The author concludes that the condition is neither an inflammation nor a tumor, but is a fibroepithelial proliferation that begins locally in the mammary tissue, and afterward extends diffusely over the whole mamma, with a tendency to bilateral occurrence. With the increasing development and irregularity there are formed multiple cysts, and in addition occasional independent multiple tumors such as papillomata of the milk ducts, fibroadenomata, cancer (and possibly, sarcoma). The disease can probably retrocede in the initial stages, but in its later stages it is hardly possible, especially when tumors are present.

In 52 per cent of the cases there was no histologic evidence or

suggestion of cancer; in 24 per cent there were appearances that might be interpreted as incipient cancer, and in 10 per cent histologic infiltrating cancer was present.

In 140 cases of carcinomatous breasts 60 per cent showed definite fibroadenomatosis of the noncancerous portions. Reasoning from the appearances found in his material, the author comes to the conclusion that "mammary cancer occurs up to 80 per cent as a secondary process in relation to fibroadenomatosis in one of its various forms."

He sees an analogy between what goes on in the mucous membranes of the mouth, throat, urogenital tract, and so forth, where there is a precancerous development of fibroepithelial papillomata, that afterward become cancerous and fibroepithelial growth with papillomata in the mamma. Fibroadenomatosis mammæ, therefore, must be conceived of as a precancerous condition, though all cases do not necessarily develop into cancer.

It is impossible to make an accurate differential diagnosis between "benign" and "malignant" cases, therefore the treatment is difficult. In young patients the excision of local areas may be sufficient, but in older ones, amputation of the breast may be better. It is inevitable that numerous breasts will be removed, in which no malignant change will be found, but such sacrifice is deemed justifiable.

J. McF.

RECENT ADVANCES IN NEUROLOGY. By W. RUSSELL BRAIN, M.A., D.M., M.R.C.P., Assistant Physician to the London Hospital; Assistant Physician to the Hospital for Epilepsy and Paralysis, Maida Vale, and E. B. STRAUSS, B.A., M.B., B.CH., M.R.C.P., Medical Registrar to the Hospital for Epilepsy and Paralysis, Maida Vale; Clinical Assistant to the Medical Department, King's College Hospital. Pp. 412; 38 illustrations. Philadelphia: P. Blakiston's Son & Co., 1929. Price, $3.50.

THE value of Pavlov's conditioned reflex is emphatically stated. From late studies of the tuber cinereum it is hinted, "the nervous system acts as an unsuspected integrator of many metabolic and endocrine functions." Various new "diseases" are considered. To mention some—dystrophia myotonica, erythroedema, epiloia and pyknolepsy. Refreshing optimism is shown in treatment and Roentgen rays are said to be helpful in new growths—even syringomyelia, neuralgias, inflammatory and infectious diseases of the central nervous system, certain "functional" nervous conditions and some traumatic lesions. The twelve appended cerebrospinal fluid "pictures" are helpful.

This excellent book is destined to fulfill the needs of those seeking recent advances in neurology. N. Y.

THROMBOANGIITIS OBLITERANS—CLINICAL, PHYSIOLOGIC AND PATHOLOGIC STUDIES. By GEORGE E. BROWN, M.D., and EDGAR V. ALLEN, M.D., Division of Medicine, Mayo Clinic, Collaborating in PATHOLOGY with HOWARD R. MAHORNER, M.D., Fellow in Surgery, The Mayo Foundation. Pp. 219; 62 illustrations. Philadelphia and London: W. B. Saunders Company, 1928. Price, $3.00.

AN excellent presentation of the clinical and pathologic picture of thromboangiitis obliterans, the problems of diagnosis, and the indications for, and methods of treatment: based on an experience of over 300 cases seen in the Mayo Clinic and on a thorough survey of the literature. It is significant that in this malady a satisfactory result may often be obtained by treatment measures other than amputation, provided that the diagnosis be made sufficiently early. The reader will, therefore, find especially useful the discussion of the differential diagnosis of this condition from other forms of arterial disease, notably Raynaud's disease, erythromelalgia and arteriosclerosis.

R. K.

THE BIOCHEMISTRY OF THE AMINO ACIDS. By H. H. MITCHELL and T. S. HAMILTON. The University of Illinois. Pp. 619; 21 illustrations. American Chemical Society Monograph Series. No. 48. New York City: The Chemical Catalog Company, Inc., 1929. Price, $9.50.

THIS book is a much needed review of the present status of research on the rôle of amino acids in animal metabolism. Of the ten chapters in the book all are devoted to various phases of amino-acid metabolism except the first three which cover physical and chemical properties of amino acids and methods for their determination, both separately and in hydrolytic mixtures. The opening chapter on physical and chemical properties is unfortunately somewhat marred by lack of completeness and occasional inaccuracies.

The authors, as indicated in their preface, make a definite attempt to present a survey of past research in the field of amino-acid metabolism with especial emphasis on the critical weighing of divergent conclusions of different investigators, and to pass judgment in such cases as to their relative values. Perhaps one of the most valuable features of the book is its insistence on the quantitative side of nutritional studies. The authors set up a rigorous standard for the quality of proof required for definite conclusions. These requirements, if taken seriously by nutritional workers should do much to bring order out of the comparative confusion now existing.

J. A.

INJECTION TREATMENT OF INTERNAL HEMORRHOIDS. By MARION C. PRUITT, M.D., L.R.C.P., S. (ED.), F.R.C.S. (ED.), F.A.C.S. Pp. 137; 9 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $3.00.

THIS little book gives an admirable presentation of the subject of hemorrhoids. Several chapters are given over to the anatomy, etiology, pathology and symptomatology as well as treatment. Unbiased quotations from recognized authorities are frequently used for and against both surgical and injection treatment.

The injection treatment is described in detail and advanced for almost general use. The author acknowledges that recurrence after injection is probably more frequent than after surgery, but he argues that the injected patient will return for a second treatment whereas the patient treated by operative surgery is frequently deterred because of his previous painful experience.

The work is interesting and instructive. E. E.

THE CLIMACTERIC. (THE CRITICAL AGE.) By GREGORIO MARANON, Professor of Medical Pathology in the Madrid General Hospital. Translated by K. S. STEVENS. Edited by CAREY CULBERTSON, A.B., M.D., F.A.C.S., Associate Clinical Professor of Obstetrics and Gynecology, Rush Medical College. First American edition from second Spanish edition. Pp. 425; 18 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $6.50.

A PERUSAL of this book quickly demonstrates that it is concerned with a much broader subject than the mere cessation of the menses. The author differentiates clearly between the menopause, which is merely a simple genital incident in woman and the climacteric, occupying a long period of life, the nucleus of which is the genital subsidence, but in the development of which all organic activities participate. An interesting section is devoted to the critical age in the male. The scattered editorial comments of Culbertson are quite acceptable to readers of this American edition. The work is encyclopedic in character, presents some interesting theories and can be recommended as a reference book. F. B.

YOU AND THE DOCTOR. By JOHN B. HAWES, 2d, M.D. Pp. 181. Boston and New York: Houghton Mifflin Company, 1929. Price, $2.00.

IT is perhaps fortunate for the conscientious members of the medical profession that they are not apt to be aware of the degree to

which their aims and aspirations are misunderstood by the general public. Granted the truth of such an unwelcome state of affairs, the benefit of such a book as the one under review to the medical profession, as well as to the public is obvious. And if the type of book is desirable, it is doubly so when written by such a sound conservative authority as Dr. Hawes, who, as the blurb tells us, is "a famous doctor . . . of great reputation." To make assurance doubly sure the book has been censored by six friendly experts and launched with an approving introduction by Dr. R. C. Cabot. While it will probably most frequently be found where it is least needed—in the doctor's waiting room—it is to be hoped that it may be possible to circulate it among those who wait too long for medical aid. "Call the doctor at once" is the chief refrain and properly so for the conditions discussed. Perusal of the greater part of the book offers much sane advice to commend, nothing to object to, and but few important omissions—a hypercriticism at best in such a work.

E. K.

A Manual of External Parasites. By Henry Ellsworth Ewing, Ph.D., United States Bureau of Entomology, Washington, D. C. Pp. 225; 96 illustrations. Springfield, Ill.: Charles C. Thomas, 1929. Price, $4.50.

A taxonomic summary of the five major groups of ectoparasitic arthropods: The mites, ticks, biting lice, sucking lice and fleas. Keys are given, in most instances, to the known genera of the world, and are supplemented by figures of important species. Descriptions of new genera, proposed in the text and included in the keys, are given in an appendix. The author has also included short discussions of life histories, natural relationships, geographical distribution, parasitic habits and economic importance of the various groups, and has added practical suggestions for control.

H. R.

The Clinical Aspects of Venous Pressure. By J. A. E. Eyster, B.Sc., M.D., Professor of Physiology, University of Wisconsin and Associate Physician, Wisconsin General Hospital. Pp. 135; 7 illustrations. New York: Macmillan Company, 1929. Price, $2.50.

Though adequate indirect methods for measuring the venous blood pressure have now existed for over twenty years, this clinical test has received but little attention in this country, except from the Wisconsin group of which the author is a prominent member. And yet it has been repeatedly demonstrated that it is a valuable clinical

method; often, for instance, demonstrating an approaching cardiac failure before any other signs are positive. The present booklet, then, small, inexpensive, easily comprehended and written by an acknowledged authority on the subject, is a welcome and valuable addition to our medical literature and one that merits a wide distribution. When one considers the importance of chronic passive congestion of the viscera in heart disease, both in its direct effect on the condition of the patient as well as an indication of the cardiac efficiency at the moment, it is not too much to say that venous pressure should be followed in cardiac cases as routinely as is the arterial pressure today. Eyster's book will tell you how easily it can be estimated and the significance of the results found. Such typographical errors as "parthenthesis" (p. vii), "Reynaud" (p. 13), "Haidenhein" (p. 15), "Samana" (p. 134) indicate a certain amount of regrettable carelessness in the proof reading that was fortunately not present in the writing. E. K.

BOOKS RECEIVED.

NEW BOOKS.

*The Principles of Clinical Pathology in Practice.** By GEOFFREY BOURNE, M.D. (LOND.), M.R.C.P. and KENNETH STONE, M.D. (OXON.), M.R.C.P. Pp. 392; 10 illustrations. New York: Oxford University Press, American Branch, 1929.

*Surgical and Medical Gynecologic Technic.** By THOMAS H. CHERRY, M.D., F.A.C.S. Pp. 678; 558 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $8.00.

*Minor Surgery.** By FREDERICK B. CHRISTOPHER, M.D. Pp. 694; 465 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $8.00.

*Some Principles of Minor Surgery.** By ZACHARY COPE, M.S., M.D. (LOND.), F.R.C.S. (ENG.). Pp. 159; 82 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $3.50.

*Endocrine Disorders.** By PROF. HANS CURSCHMANN. Pp. 188; 46 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $4.00.

*Sterilization for Human Betterment.** By E. S. GOSNEY, B.S., LL.B. and PAUL POPENOE, D.Sc. Pp. 202. New York: The Macmillan Company, 1929. Price, $2.00.

*An Introduction to Pharmacology and Therapeutics.** By J. A. GUNN, M.D., D.Sc. (EDIN.), M.A. (OXON.). Pp. 220. New York: Oxford University Press, American Branch, 1929.

* Reviews of titles followed by an asterisk will appear in a later number.

*Rickets Including Osteomalacia and Tetany.** By ALFRED F. HESS, M.D. Pp. 485; 52 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $5.50.

*Tuberculous Intoxications.** By JOSEPH HOLLÓS, M.D. Pp. 132. New York: William Wood & Co., 1929. Price, $3.25.

*James Mackenzie Institute for Clinical Research. Gastro-Intestinal Diseases.** Edited by PROF. DAVID WATERSTON, M.A., M.D., F.R.C.S. (EDIN.). Pp. 278; 13 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $3.25.

*Varicose Veins.** By H. O. MCPHEETERS, M.D., F.A.C.S. Pp. 208; 34 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $3.50.

Abstracts, Proceedings of Meetings of New York Pathological Society, 1927–1928. Pp. 71.

Dedication of the Montgomery Ward Memorial Building Northwestern University Medical School. Pp. 193; illustrated. Chicago: Northwestern University Press, 1929.

Combined Sinus and Duodenal Infections. By S. PESKIND, B.S., M.D. Pp. 20. Privately printed, S. Peskind, Cleveland, Ohio.

*Outline of Preventive Medicine.** Twenty-one contributors. Pp. 398. New York: Paul B. Hoeber, Inc., 1929. Price, $5.00.

*Practical Handbook for Diabetic Patients.** By ABRAHAM RUDY, M.D. Pp. 180; 7 illustrations. Boston: M. Barrows & Co., 1929. Price, $2.00.

United Fruit Company Medical Department, Seventeenth Annual Report, 1928. Pp. 381; illustrated. Boston: United Fruit Company, 1929.

*The Common Head Cold and Its Complications.** By WALTER A. WELLS, A.M., M.D., F.A.C.S. Pp. 225; 15 illustrations. New York: The Macmillan Company, 1929. Price, $2.75.

NEW EDITIONS.

Medical State Board Questions and Answers. By R. MAX GOEPP, M.D. Pp. 754. Sixth edition. Philadelphia: W. B. Saunders Company, 1929. Price, $6.00.

A Study of Masturbation and The Psychosexual Life. By JOHN F. W. MEAGHER, M.D., F.A.C.P. Second edition. Pp. 130. New York: William Wood & Co., 1929. Price, $2.00.

Diseases of the Chest. By GEORGE WILLIAM NORRIS, A.B., M.D. and HENRY R. M. LANDIS, A.B., M.D., Sc.D. Pp. 954; 478 illustrations. Fourth edition. Philadelphia: W. B. Saunders Company.

A first class book welcome in each new edition. In this fourth edition a chapter on the transmission of sounds through the chest by C. M. Montgomery has been added; also a brief account of bronchoscopic diagnosis by L. H. Clerf.

Pathogenic Microörganisms. By WILLIAM H. PARK, M.D., ANNA WESSELS WILLIAMS, M.D. and CHARLES KRUMWIEDE, M.D. Ninth edition. Pp. 819; 225 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $6.50.

A deservedly well-known book. The chief developments of the past three years have been included (scarlet fever, measles, yellow and undulant fevers, tularemia, new types of pneumococci, etc.).

* Reviews of titles followed by an asterisk will appear in a later number.

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The Arterioles in Cases of Hypertension.—Biopsy is becoming more and more to be utilized not only by the surgeons but by clinicians as well in various types of studies of living tissue. One of the most interesting results from the examination of biopsy material is presented in an article by KERNOHAN, ANDERSON and KEITH (*Arch. Int. Med.*, 1929, **44**, 395). These investigators studied the arterioles of muscle tissue removed from the pectoralis major of patients suffering from hypertension. Muscle tissue was utilized because it makes up over one-third of the body mass and it seems fair to assume that if the arterioles are involved by pathologic changes it certainly would be possible to demonstrate such alterations from the normal in the bloodvessels of muscle. After a thorough review of the pertinent literature relative to the study of the small bloodvessels, the results of the findings are recorded in the three types of hypertension in which the arteriolar condition was investigated: (1) Benign hypertension; (2) an intermittent group presenting the syndrome of severe benign or early malignant hypertension; (3) malignant hypertension. From the point of view of the clinical manifestations of the condition, it might be said that the maximal blood pressure in benign cases was 240 systolic and 145 diastolic. In the intermittent group it was 280 systolic and 160 diastolic; in the malignant type it was 320 systolic and 180 diastolic. Cardiac hypertrophy, peripheral sclerosis, retinal sclerosis, albuminuria, evidences of renal insufficiency and anemia were also noted, all these customary findings naturally being much less pronounced in the benign cases than in the other two groups of cases. The authors worked out a scheme for determining the relation of the vessel wall to the lumen of the arteriole. Normally this ratio is as 1 to 2. In the cases of benign hypertension the average ratio was 1 to 1.4 with a variation of from

1 to 1.4 to 1 to 1.8. The intermittent and the malignant hypertension ratio for the wall of the lumen was practically the same. The authors do not believe that it is possible to distinguish the special types of hypertension from histologic study of fresh tissue. The study indicates definitely that there is associated with hypertension a diffuse disturbance of the arterial vascular system. In the great majority of cases the malignant syndrome does not develop. The authors state that any possible theory as to the cause of diffuse vascular hypertensive disease must explain the slow progress in benign hypertension, the rapid development of the course of malignant hypertension, and the gradual transition from benign to malignant hypertension in some cases of chronic nephritis. They suggest two general possibilities as the cause of the condition: (1) An inherent disturbance in the nervous system, or (2) the action of an hypothetic pressor substance on the sympathetic chain, on sympathetic endings in the wall of the arteriole or directly on the smooth muscle of the wall.

The Incidence of Infection with Endamœba Histolytica in Louisiana as Determined by Comparative Microscopic and Cultural Methods.—Johns and Tripoli (*New Orleans Med. and Surg. J.*, 1929, **82**, 224) write that the incidence of infection with Endamœba histolytica necessarily would represent not only those who are suffering from the active manifestations of amebiasis, but also a still larger number of individuals who are carriers of the infective cysts. On account of the difficulty of making large series of examinations, it has been impossible to make surveys of the general population for carrier incidence as well as for the frequency of amœbas. This is really a problem of importance, bearing in mind that the disease has not decreased as have other enteric diseases with the institution of modern sanitary handling of water and milk. Also, it should be remembered that the carrier is producing and discharging an enormous number of parasitic cysts and that potentially he is not only likely to develop active symptoms, but also liver abscess may develop in an individual who is a carrier without the occurrence of symptoms of active dysentery. The authors' study represents a series of 554 examinations, the stools being examined both directly following passage by the centrifuge-concentration method and by the utilization of a special method of culturing the feces. In the majority of cases only one specimen was examined, but it is believed that the great majority of infections may be demonstrated from the preliminary or original examination. Incidentally, it has been found that the direct examination of the stools and culturing the stools give figures which are approximately identical. It was found that 36, or 7.44 per cent, of the individuals were infested with Endamœba histolytica. Dividing these individuals into groups, it was found that in private patients to the number of 130, 6.92 per cent were infected. Of 180 medical students, 8.33 per cent and of 234 patients in Charity Hospital 7.22 per cent were infected. In only 1 per cent of the infected individuals were there any definite symptoms of dysentery or were the vegetative forms of the parasite present. Considering the three sources from which the specimens were obtained, the authors felt that 7.44 per cent represents a fair index of the infection in this particular state in the South.

SURGERY

UNDER THE CHARGE OF

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Cholecystography.—ROBINS (*New England J. Med.*, 1929, **201**, 114) states that the sudden impetus in the advancement of knowledge regarding gall-bladder physiology must be attributed to cholecystography. The emptying and concentrating function of the gall bladder was little understood. Graham believes that the gall bladder is emptied by the elastic recoil of the distended viscus on release of the common duct sphincter, the inflow and outflow of bile from the liver through the periodic closing and opening of the sphincter, and suction due to the stream of bile from the liver as it passes the mouth of the cystic duct. The basis of his arguments is that the gall bladder has never been seen to contract spontaneously. Experimental evidence lends very little support to the effect of respiration. Another important function is the concentration of bile. This is the fundamental reason why cholecystography is feasible. Rous and McMaster showed that the gall bladder could concentrate the bile seven times or more in twenty-four hours, the process being accomplished by osmosis and diffusion. The technique of cholecystography must be exact. Care must be taken that the patient holds his breath during the exposure of film. The slightest motion may lead to erroneous conclusions. The normal gall bladder is densely outlined and is oblong or pear shaped. It should empty completely or contract to about one-third of its original size two hours after a fat-protein meal. Pathologically, gall bladders may be divided into three groups: Disease of the mucous membrane; disease of the muscle and change of the serosa. He takes up the reasons for failure to visualize the gall-bladder shadow.

Variations in the Extra Hepatic Biliary Tract.—BEAVER (*Arch. Surg.*, 1929, **19**, 321) says that the normal angular mode of juncture of the cystic duct with the hepatic duct, as described in textbooks of anatomy occurred in only a little more than half of the cases. The long and short parallel types of cystic duct occur in more than a third of the cases and, as is shown by the literature, is perhaps the most common cause of accidents in biliary surgery. In such cases there is a marked increase in the length of the cystic duct and a corresponding decrease in that of the common bile duct. The cystic duct and the hepatic duct are so intimately bound together by fibrous tissue that they are absolutely inseparable and thus appear as a single duct. Any rough manipulation may tear the thin septum which exists between them. The large portion of a cystic duct of this type which remains following cholecystectomy may dilate and form a new gall bladder, probably with recurrence of symptoms. The cystic duct does not contain valves of Heister in the portion which lies parallel to the hepatic duct. It has been recorded

that strong traction on the gall bladder is much more likely to tear off a spiral cystic duct than a duct with a normal arrangement. Accessory hepatic ducts occurred in 5 cases or 8.7 per cent of this series. Four of these were accessory right hepatic ducts 3 of which were also accessory to the cystic duct. The length and diameter of the accessory ducts corresponded closely to the normal cystic duct.

Hyperglycemia Following Head Injuries.—Mock and De Takats (*Ann. Surg.*, 1929, **90**, 190) state that head injuries of sufficient severity to cause loss of consciousness result constantly in hyperglycemia, which subsides within the first day or a few days. This has been found in animal experiments and in a small number of clinical cases. Section of the splanchnic nerves in the dog abolished this hyperglycemia. The sympathetic discharge originating in the higher centers of sugar regulation is unable to reach the liver and mobilize glycogen. This state of sympatheticotonia manifesting itself in increased epinephrin susceptibility was tested in patients shortly after and many months after head injury. While the immediate response was stronger than in controls, the late curves were mostly negative with the exception of those who had marked residual damage. A few patients were found whose epinephrin curve was not abnormally high, but showed a delay in returning to normal. These patients were all above forty years of age and may have mild pancreatic damage. This is not uncommon at this age and deserves careful consideration. Theoretically the possibility of upsetting an already weakened pancreatic activity by a sudden sympathetic discharge, followed by a marked rise in blood sugar must be considered.

Acute Fractures of the Shaft of the Femur in Children.— Conwell (*J. Bone and Joint Surg.*, 1929, **11**, 593) declares that there is unlimited literature on fractures of the femur in children. Plaster cast, plaster cast and extension, and suspension and extension, are the main forms of treatment. Excellent results are obtained by various surgeons by all of the above methods. The suspension and extension method is the most popular. Treatment by open reduction should be the last resort and usually is not necessary. A summary of the results of the cases treated by plaster cast shows that better results are obtained in the very young than in the older child. A summary of the cases treated in plaster cast and extension shows that better results are obtained in the older child. Careful physical and radiologic examinations with careful history of the accident should always be made. Immediate reduction with aid of fluoroscope should be done. Every case of fractured femur should be considered an emergency and immediate treatment should be given following injury. Good alignment is most important, then bone approximation. It is definitely concluded that compensatory lengthening does take place, also correction of poor alignment, but chiefly in patients before the age of eight years. The suspension and extension method is by far the most comfortable dressing, and best results have been obtained by this method. Granting that compensatory lengthening does take place and that serious misalignments are corrected in fractures of the femur in children, no surgeon is justified in neglecting anyone of the important things which should be done immediately following a fracture of the femur.

THERAPEUTICS

UNDER THE CHARGE OF

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Treatment of Hay Fever.—According to VON LEEUWEN (*Therap. d. Gegen.*, 1929, **70**, 244), patients who show manifestations of hay fever throughout the year (rhinitis vasomotoria) should be separated from the ones with true hay fever caused by pollens. The sensitivity of the skin and mucous membranes to pollens is parallel. The author prefers the cutaneous test to the intracutaneous one as the latter may induce marked systemic reactions. The cutaneous test is performed by inducing a small scarification of the skin and rubbing in 1 to 2 drops of pollen extract. With a positive reaction a wheal with a surrounding flare develops within five to ten minutes. For general practice it is sufficient to use two mixtures of extracts. One of the extracts is a mixture of a number of grains and the other is a mixture of various weeds. In the treatment of hay fever the most important measure is the preventive one. The patient should avoid exposure to pollens as much as possible. Complete desensitization cannot be achieved; one can expect but a reduction in sensitivity. In the desensitization, specific and nonspecific agents are applied. Among the nonspecific agents the author prefers the tuberculin therapy. Patients with allergy show a strongly positive von Pirquet reaction. The injection of tuberculin has a beneficial influence on both asthma and hay fever. The treatment for hay fever starts usually in March or April; the initial dose is 0.1 cc. of a dilution of 1 to 100,000. The injection is repeated three times weekly; the dosage increased by 0.1 cc. with each injection. When a total dose of 1 cc. is reached the injections are continued with a dose of 0.1 cc. of a dilution of 1 to 10,000. With the onset of strong local or general reaction the treatment is discontinued for a week, after which it is resumed again, starting with a smaller dose and gradually raising the amount injected. With the onset of the hay fever season only one injection is given a week and the dosage is not raised. After the season is over the injections are discontinued until they are resumed in the next season. Tuberculin therapy alone is insufficient to induce marked reduction in sensitivity in the majority of cases, and additionally specific therapy is used, according to whether the patient is sensitive to grain mixtures or weed mixtures. A solution containing a mixture of grains or weeds is injected with an initial dose of 0.5 cc. of 1 to 1,000,000. The injections are continued with gradually increasing doses three times a week. If mild reaction (conjunctivitis or rhinitis)

develops the treatment is discontinued for two or three days, then it is renewed in smaller amounts and the dosage is raised cautiously. Development of neuritis contraindicates the treatment instantly. With the onset of the hay fever season, the amount injected should not be further raised. Individual sensitivity may alter the amounts to be administered considerably. Even after successful desensitization the positive skin reaction persists, though with less intensity. Among the therapeutic measures which are useful in the treatment of hay fever, following its clinical manifestation, are adrenalin, ephedrin and aspirin. The application of paraffin in form of salves over the mucous membrane and the protection of the eyes against light by wearing dark glasses may also be beneficial. The intravenous administration of calcium chloride is also advocated.

The Treatment of Exophthalmic Goiter.—The spontaneous recoveries of patients with exophthalmic goiter make the evaluation of therapeutic measures difficult. A critical study is presented by Don (*Brit. Med. J.*, 1929, **i**, 1108) on the relative value of: (1) rest combined with iodine; (2) Roentgen ray therapy; (3) operative procedure.

The effects of iodin were observed in 36 cases in which the rate of the basal metabolism varied between +30 and +114 per cent. Lugol's solution was given in doses of 20 to 30 minims a day. Definite temporary improvement followed this treatment in 84 per cent of the cases. In 16 cases the effect of a second course of treatment was studied. In only 37 per cent of the cases was a second course equal to the first in effectiveness. The maximal fall in the basal metabolism and the pulse rate was reached in ten to fourteen days. Iodin itself cannot cure exophthalmic goiter, and therefore it should be held back until operation is decided upon. Iodin is an excellent therapeutic agent for thyroid crisis with vomiting, but if a course has already been given, its value may be disappointing. During the iodin administration the patients often gain weight.

There is still considerable skepticism concerning the value of Roentgen ray therapy. The effect of Roentgen ray therapy was investigated in 23 patients with exophthalmic goiter and with a basal metabolism more than +30 per cent. Treatments were given at first twice a week, then once a week, and the intervals were gradually lengthened until a total of about 30 doses (one dose equal to a quarter of an erythema dose) were administered over a year. In 12 of the cases there was either a cure or marked improvement. This improvement was obvious in most cases by the third month, and in all cases by the sixth month. If no signs of improvement are present at the end of the sixth month, it is doubtful if further Roentgen ray therapy will be of benefit. Cases with short history of the disease and small goiter had the best tendency to benefit by Roentgen ray treatment.

The merit of the operative treatment was tested on 25 patients, after preparation with Lugol's iodin, 10 minims three times a day. Operation was performed only if the basal metabolism was under +30 per cent. Thyroidectomy was performed on 21 patients. Eighty per cent of the patients operated on became cured, or considerably benefited for at least one year after operation. It cannot be too strongly emphasized that surgical intervention should only be undertaken by an

experienced surgeon. Operative treatment is the most effective therapy for exophthalmic goiter.

Don concludes that the patient should be given six months' trial with Roentgen ray therapy; then, if improvement does not occur, the patient should be sent to an experienced surgeon for operation if the case is suitable.

PEDIATRICS

UNDER THE CHARGE OF

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Successive Roentgenograms of the Chest of Children During Measles.—KOHN and KIORENSKY (*Am. J. Dis. Child.*, 1929, **38**, 258) had successive roentgenograms of the chest taken in 30 children between the ages of seven months and twelve years in the various stages of measles. Infiltrations of the lung was seen for the first time in the pictures in the preëruptive, eruptive and posteruptive stages. These were present in 62.4 per cent of the patients less than four years of age and in 42.2 per cent of the patients four years or over. In those cases showing pulmonary infiltration, this was present in 61 per cent of the cases before or during the height of the eruption. The infiltrations were of three types; large, homogenous triangles; large homogenous opacities obscuring the hilum and the paravertebral regions; and disseminated, confluent, fine and coarse mottling in various areas of the lung field. For the latter type a common site was in the cardiophrenic angles. The most infrequent site was the right lower lobe; the right upper, the left lower, the right upper and right middle lobes following in the order given. The infiltrations were most dense during the receding eruptive or posteruptive stage. In 27 cases shadows suggesting infiltration of the lung appeared and continued to progress after the temperature of the child was normal. In these cases there were no definite physical signs. In the group in which no pulmonary infiltration was seen 79.2 per cent of the patients gave clinically mild courses of measles while in those cases in which pulmonary infiltrations appeared in the pictures 44.4 per cent were mild. Physical signs of bronchial or pulmonary involvement were present in 14 per cent of those which showed no pulmonary infiltration on the roentgenogram and in 47 per cent of those which did show pulmonary infiltration. It was impossible to predict from the physical examination during the eruptive stage which cases would show pulmonary infiltration in the roentgenogram. Abnormal intensity of the pulmonary markings was present in 80 per cent of all cases. Their appearance in the plates in children four years and over was somewhat different from those in children less than four years.

The Effect on Digestion and Assimilation of Including Bananas in Mixed Diet of Children Over Five Years of Age.—BROWN and COURTNEY (*Can. Med. Assn. J.* 1929, **21**, 37) studied children between the

ages of five and thirteen years of age in groups of 4, having 2 on a mixed diet without bananas and 2 on the same diet with from three to six bananas substituted for an equivalent amount of carbohydrate. After a suitable interval the diet of the two pairs were transposed. A preliminary period on a measured food intake was followed by the taking of representative samples of the diet and the fecal and urinary output of each child were collected over a four-day period. This material was analyzed for the content of fat, nitrogen, total ash, calcium, magnesium, phosphorus and chlorid. The moist and dried weight of the feces and the volume of urine were noted daily and the hydrogen-ion concentration was estimated in the fresh urine and feces. The percentage of intake retained was taken as the standard of digestion and assimilation. In respect to nitrogen retention the difference was somewhat greater than for the other components determined, but it is questionable whether this difference is sufficient to be of any significance. The averages for the group periods showed small differences, sometime to the advantage to the banana-containing diet and sometime to that of the control diet. There was always a somewhat greater output of feces during the banana feeding than during the controlled diet, but there never was any diarrhea on the banana diet. The urine was always distinctly more alkaline with the banana-containing diet than with the control diet as shown by the hydrogen-ion values. This suggests, that the banana may be of value for addition to diets in acid conditions.

The Status of the Therapeutics of Irradiated Ergosterol.—Hess, Lewis and Rivkin (*J. Am. Med. Assn.*, 1929, **93**, 661) after further clinical experiments state that preparations of irradiated ergosterol is specific for rickets, tetany and osteomalatia. It has not been proved of definite value in other clinical conditions. During the past year the dosage has been established for the prevention and cure of rickets. Premature and exceptionally rapid growing infants may be regarded as a separate group and the dosage gauged according to a different scale. The basis of this standardization is a biologic estimation of the antirachitic potency rather than a gravimetric assay of the irradiated ergosterol. It was found that if the prescribed dosage is observed toxic symptoms and hypercalcemia need not be feared. These phenomena seem to be entirely or almost entirely due to an excess of antirachitic action. Hypercalcemia also can be produced experimentally by giving undue amounts of cod-liver oil. Irradiated milk, especially dried milk is also a valuable product in combating rickets and tetany and most especially in their prevention. It is not believed that irradiated cereals will play any rôle in the control of rickets because of the numerous technical difficulties involved in the course of activation, such biologic products as irradiated erogsterol and irradiated foods should be subject to careful laboratory control.

The Intermuscular Injection of Adult Whole Blood as Prophylaxis Against Measles.—Bader (*J. Am. Med. Assn.*, 1929, **93**, 668) used from 20 to 30 cc. of the whole blood of persons recovered from measles in 30 patients from six months to forty-two months of age. The donors had recovered from measles from two to twenty-five years before the

treatment. This blood which was given within the first seven days following exposure completely protected 12 patients insofar as the escape from measles is a proof of protection. It was followed in 9 cases by a modified and attenuated type of measles without catarrhal symptoms. In 8 patients mild catarrhal symptoms were present. One child had measles of moderate severity and she was the only one of the 30 cases which showed Koplik spots and a typical eruption. In the others in whom there were eruptions these were not characteristic. In all but 2 cases there was distinct modification of temperature. In all except possibly 4 cases there was an apparent prolongation of the period of incubation. No complications developed. From this study it would seem that whole blood from adults even long recovered from measles is an effective measure against measles. It is suggested that it might be completely efficacious for institutions where many cross infections are found when the serum from recently convalescent patients is not readily available, or in the age group under five years in which 90 per cent of the deaths from measles occur, or in the weak and debilitated where measles might end fatally.

The Leukocyte Picture in Measles.—OLECHNOWIEZ (*Rec. Franc. de. Ped.*, 1929, **5**, 209) made 274 examinations of the blood in 32 infants and children ill with measles. He found that the leukocyte picture was a valuable aid in the diagnosis and prognosis. He found that the kind and number of leukocytes in measles vary. In the incubation period hyperleukocytosis and slight displacement of the neutrophils to the left are present and eosinophilia is common. In the period of invasion there are leukopenia and displacement of the neutrophils to the left in the benign cases in which the prognosis is given, and hyperleukocytosis, hyperlymphocytosis and a decreased number or absence of monocytes and eosinophils in the severe cases in which the prognosis is bad. In the posteruptive period there are slight leukocytosis, slight lymphocytosis or normal lymphocythemia and an increased number of eosinophils and monocytes. In measles in children of less than four years of age the leukocyte picture is variable.

The Immunologic Researches on Whooping Cough.—DEBRÉ, MARIE and PRÉTET (*Ann. de. med.*, 1929, **25**, 434) studied colonies of Pertussis bacilli obtained by cultivating droplets from patients with whooping cough. In this manner they isolated and cultivated a large number of strains of Pertussis bacilli. They attempted to determine whether or not these strains belonged to the same type and they found that none of the bacilli was agglutinated by experimental serum A, while bacilli of the control culture were agglutinated by this serum in concentration of 1 to 1000. The bacilli of all of the strains were agglutinated with serum B, most of them at a concentration of 1 to 1500 or 1 to 1000. The bacilli of the control culture did not show agglutination to this serum. The bacilli of only 5 of the cultures were agglutinated by therapeutic serum of Bordet-Gengou. The agglutinating serums agglutinated bacilli of all the strains at concentrations varying of from 1 to 500 to 1 to 4000. Only bacilli of the control culture were not agglutinated. This study showed that the strains of bacilli studied were of a homogeneous nature.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Nonvenereal Affections of the Genitalia.—SEMON (*Brit. J. Ven. Dis.*, 1929, **5**, 144) discusses conditions of the genitalia commonly seen by the dermatologist. Chief among local expressions is the occurrence of eczema usually as moist intertrigo. Occasionally eczema is associated with thread-worms, rectal fissures or an underlying mycosis. A chronic dry pruritic form is of neurogenic significance. Psoriasis may appear on the genitalia as its sole localization, and as such is important in differential diagnosis from the nonulcerative late syphilide. Lichen planus of the penis is usually nonpruritic and may persist for months or years. Urticaria in the form of Quincke's edema is prone to attack the scrotum or a single labium majus. It is painless, afebrile and unaccompanied by glandular swelling, all of which should protect the patient from surgical intervention. Its sudden onset and history of previous attacks is likewise characteristic. The author has used intravenous injections of afenil (calcium-urea compound with good success. Medicinal eruptions include the genital reactions to antipyrine and phenolphthalein and the lesions of dermatitis venenata resulting from petroleum products, quinin in pessaries and certain mercurial ointments. Erythema multiforme and pemphigus frequently present their primary signs on the genitalia in the form of bullæ and often ulcers. Anogenital pruritus includes patients in two main categories, the well-nourished, opulent middle-aged man of sedentary habits and the nervous high-strung woman of temperate and otherwise blameless disposition. Frequently fungi can be demonstrated in this type of case, and in a high proportion relief is obtained by the empirical use of fungicidal ointments. Pediculi and scabies are important, quite as much as a result of improper measures sometimes employed in their treatment as because of the disease itself. Herpes genitalis and condyloma acuminatum appear to be conveyed by sexual intercourse and are often confused with more serious conditions. Molluscum contagiosum may assume the gigantic type, occasionally is subject to secondary infection and frequently remains unchanged for years. Important among the nonvenereal ulcers are those due to mechanical, chemical or thermal trauma; the acute tuberculous ulcer, the diphtheritic ulcer and the gangrenous ulcer of varied etiology.

Dr. T. Anwyl Davies, in discussing the author's paper, emphasized the Trichomonas vaginalis as a not uncommon cause of vaginitis. This parasite appears to become pathogenic in the presence of other organisms favoring its growth. Dark-field examination is the best method to demonstrate its presence in the secretion. The patients

complain of a severe irritation and a greenish discharge. Mild alkaline douches readily clear up this type of vaginitis. Dr. Doble referred to two cases of ulceration of the genitalia that were cured by the use of an autogenous diphtheroid vaccine.

The Spirocheticidal Activity of the Human Syphilitic Serum and the Immunologic Significance of the Wassermann Reaction.—KOLMER and RULE (*Arch. Derm. and Syph.*, 1929, **20**, 90) working on experimental rabbit syphilis, mixed suspensions of active Spirocheta pallida with the unheated sterile serums from both healthy nonsyphilitic individuals and syphilitic (strongly positive Wassermann) individuals. Control animals received the spirochetal suspensions mixed with saline solution. All the control animals became infected with syphilis while the animals receiving the spirochetal suspensions mixed with human syphilitic or nonsyphilitic serums did not all develop active syphilis. The fresh normal and syphilitic serums appear slightly and equally destructive for Spirocheta pallida at 37° C. *in vitro* in an exposure of two hours as compared with a physiological solution of sodium chlorid.

Further experimental studies were done to determine the effect of human syphilitic (strongly positive Wassermann) and nonsyphilitic serums *in vivo* on rabbits with active syphilis. The animals were treated in two groups, one with intravenous injections of syphilitic human serum while the other group received nonsyphilitic human serum. In no instance were there any appreciable curative (spirocheticidal) effects nor a response to the nonspecific effects of serum proteins. No immunity could be obtained by injection of syphilitic human serum into rabbits prior to inoculation with spirochetal suspensions.

The authors conclude that acquired immunity in syphilis is not humoral in character and is not due to demonstrated spirocheticidal antibodies in the serum. Specific serum prophylaxis and treatment of syphilis does not occur nor is it possible by known methods. Syphilitic serum containing large amounts of complement-fixing antibody (strongly positive Wassermann) is apparently devoid of specific spirochetal activity. The presence of the complement-fixing antibody does not denote coincident presence of antispirocheticidal substance but may be an index of tissue immunity.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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The Present Status of Lead Therapy in Malignant Disease.—In view of the world-wide interest in the treatment of malignant diseases by means of the injection of lead preparations it is most welcome to the

profession to peruse the report of BLAIR BELL (*Brit. Med. J.*, 1929, i, 431) who is the chief proponent of the method. His report deals with the results obtained from November 9, 1920, to November 9, 1928, and therefore gives a good general survey of the situation. The report is as follows:

1. Total number of cases treated	566
2. Died of the disease before treatment could be completed	359
(*a*) Received less than 0.25 gm. of lead	198
(*b*) Received more than 0.25 but less than 0.5 gm. lead	161
3. Died of disease after treatment was concluded	77
4. Died of intercurrent affections, while under treatment	7
5. Died as result of extensive destruction of tissue	5
6. Complete treatment refused	22
7. Too recent for results to be estimated	31
8. Believed cured but died of other affections	2
9. Disease completely arrested	12
10. Believed cured and treatment stopped	51

Bell reminds us that in any estimate of results the serious type of case treated must be clearly remembered; it may be described as consisting largely of that in which the condition was considered hopeless. Ignoring, however, any consideration of temporary benefit, amelioration of symptoms and prolongation of life, it appears that 303 cases have to be considered (items 2 (*b*), 3, 8, 9 and 10) cases which received more than one-half of the minimum treatment advised. Seventy-seven died after full treatment, consequently it might be argued that there were 65 successes as opposed to 77 failures. Moreover he has reason to believe that at least 40 per cent of the "too recent" cases will terminate favorably. Nevertheless, to put his statistics in the worst possible light, he states that there were 65 successes out of 303 cases treated, that is 21.5 per cent of successful results. He urges the recognition of the following points relative to this form of treatment: (1) No one in his senses would care to suggest that the possession of a knife and a few instruments is all that is required for the surgical cure of carcinoma of the stomach. Yet some seem to think that for lead therapy in this disease all that is required is that lead shall be pumped into the veins of the sufferer. (2) The scientifically minded inquirer will not demand that a new method of treatment for cancer operating on the worst and most advanced types of cases shall give far better initial statistical results than those obtainable with other long established and standardized forms of treatment acting on early and selected cases; but if it should be so, those capable of appraising evidential values will appreciate the vast possibilities that await full and proper development of the method tested.

Differentiation Between Syphilis and Cancer of the Cervix.—It is well to remember that in any field of medicine syphilis may have to be considered as an etiologic factor and its ability to mimic various types of lesions has long been known. In the consideration of the differential diagnosis between syphilis and cancer when we are confronted with a lesion on the cervix, GELLHORN (*Am. J. Syph.*, 1929, **13**, 1) states that the consistency of the new growth constitutes a very valuable diagnostic criterion. A syphilitic lesion may be soft on the

surface but is always hard or firm in the depth so that the examining finger cannot penetrate deeply. This behavior is due to the fact that in syphilis the connective tissue is infiltrated and, therefore, becomes more resistant. In cancer on the other hand, there is but an apparent hardness, produced by the masses of newly formed epithelial cells, but on continued pressure, the finger can always break through into deeper layers where it encounters a soft spongy tissue. Superficial or deep disintegration is characteristic of a malignant growth. He believes that the color of the lesion is of great diagnostic imporance. Syphilitic lesions have a more or less marked yellowish discoloration which is relieved by a reddish undertone, while cancer appears a very deep red to the eye. Chancres and secondary syphilitic ulcers are almost always surrounded by a thin red line caused by new formations of capillaries. If the lesion is separated from the external os by a zone of normal mucosa the diagnosis of syphilis may be safely made. Of course, the microscopic examination usually will make the absolute diagnosis.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Iridoavulsion.—HARDING (*Penn. Med. J.*, 1929, **32**, 766) presents a case of complete loss of the iris; it is of particular interest because of the light which it will throw upon the process of accommodation. The iris had been completely torn off by a splinter of glass, so that the ciliary muscle was exposed and the ciliary body and the fibers of the zonule of Zinn could be seen plainly. Even with an ordinary ophthalmoscope it is possible to see that the body of the ciliary muscle distinctly moves forward and the lens approaches the cornea; also the periphery of the lens assumes a slightly mottled appearance which becomes smoother in distant vision. The patient, ten months after the accident, has 6/6 vision and is not bothered particularly by light, though she wears a slightly colored lens.

Ocular and Surgical Torticollis.—BRAUN (*Med. Klin.*, 1929, **25**, 590) report ocular torticollis showing none of the characteristics of surgical torticollis; degeneration of the sternocleidomastoid muscle; asymmetry of the skull and of the face; inheritability of the trouble and frequent association with other deformities; regular, rapid, cicatricial regeneration of the operatively removed sternocleidomastoid muscle. The position is assumed to restore binocular vision and most frequently results from paralysis of the superior oblique. The head is then inclined to the healthy side, bent slightly forward and turned to the healthy side; thus binocular vision is restored. Should the inferior oblique be

affected, the head is raised, turned to the healthy side and inclined to the diseased side. On the other hand, if the superior rectus is paralyzed the head is raised, turned to the side of the affected eye and inclined to the healthy shoulder. An isolated paralysis of the inferior rectus causes a bending, turning and inclination to the affected side. Treatment consists of tenotomy on the unaffected side of the proper muscle to produce compensation; for instance, if the superior oblique is affected compensation is obtained by tenotomy of the inferior rectus on the healthy side. Surgical and orthopedic measures, such as are used in surgical torticollis are absolutely unavailing. Convergent squint, nystagmus and sometimes improperly corrected astigmatism may also cause ocular torticollis.

Diagnostic Value of Isolated Pupillary Symptoms in Visceral Syphilis.—Luria (*Deutsch. med. Wchnschr.*, 1929, **55**, 1073) states that anomalies of the pupils may appear as an isolated symptom in visceral syphilis and are of importance for early diagnosis since they bear witness of the pleural-visceral nature of the disease. By anomalies of the pupil Luria does not mean those pronounced changes which indicate an involvement of the central nervous system, but slight ones which may be overlooked by the examining physician. Anisocoria, Argyll-Robertson and finally the disappearance of the sharpness and distinctness of the delineation of the iris are all isolated signs which he found variously combined and not rarely only on one side. While anisocoria appears in a number of nonsyphilitic diseases it is far more frequently associated with them. The Argyll-Robertson need not be the sharply pronounced type; lesser degrees of the condition are equally indicative. These signs are particularly excellent since they may be residua of an earlier syphilis being extremely stabile and not yielding to specific treatment; they also may occur in hereditary syphilis.

Optic Neuritis and Dental Sepsis.—Smith (*Brit. Med. J.*, 1929, **ii**, 99) reports the case of a man, aged thirty-five years, who came complaining of a "black cloud" in the outer field of his left eye. Examination showed the macula normal, but the nasal edge of the left optic disk was "fluffy." Vision in each eye was 6/6 with correction. Using the Elliot scotometer it was found that the blind spot of Mariotte was much enlarged with snail-track extensions toward the fixation point and one or two isolated scotomata. This, in conjunction with the hazy nerve head, pointed to optic neuritis. Physical examination was negative except for secretion in a tonsil, which was removed. Five days later some color perception was lost and vision had dropped to 6/12. The teeth were rayed and two proved to be suspicious; two others had pyorrhea. The four were extracted. A week later vision had improved to 6/9 and in seven weeks it was 6/6, the optic disk normal and all consciousness of the cloud gone. There can be no doubt of the relation of the dental sepsis to the optic neuritis. Smith also stresses the importance of Elliot's scotometer, since the enlargement of the blind spot and the two small scotomata would have been entirely missed by the ordinary perimeter. Without its use the significance of the slight haziness at the nasal edge of the disk would have been missed.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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The Asthma-Eczema-Prurigo Complex.—DRAKE (*Brit. J. of Dermat. and Syph.*, 1928, **50**, 407) details an account of 20 skin conditions, all of which were associated with asthma either in the patient or in his immediate family. Of these cases 14 were flexural eczema and 6 were nonflexural in type. The latter group included 1 case of infantile eczema, one case of pruritis with urticaria, one case of lichen urticatus, one nonflexural eczema, and 2 cases of ichthyosis. Most of the cases had septic foci and a small series had definite protein sensitization. All the eruptions associated with asthma were characterized by intense itching which, like asthma itself, is of paroxysmal nature. Most important in the causation, in the belief of the author, is the nervous coefficient or "make-up" of the patient. Underlying the asthma-eczema-prurigo complex is an inherent—or possibly acquired—dysfunction or dysharmony of the autonomic nervous system.

A Positive Symptom of Mastoiditis.—BERGER (*Ann. Otol. Rhinol. and Laryngol.*, 1929, **38**, 1929) calls attention to spasm and rigidity of the upper third of the M. sternocleidomastoideus as a frequent symptom of mastoiditis—especially in children or in adults with thin mastoidal cortices or whose mastoids have been perforated. The spasm and rigidity depend upon the extension of the suppurative process and "are found only when mastoid cells have undergone necrosis." The symptom is elicited best by gently palpating with the fingers of both hands and comparing both sides. It is only of significance when present.

Scalp Tenderness as an Indication of Dural Involvement in Mastoiditis.—Having observed that scalp tenderness frequently has been the chief complaint of patients with acute mastoiditis, DIXON (*Ann. Otol. Rhinol. and Laryngol.*, 1928, **37**, 1154) has found that this symptom is of value: (1) as an indication for exposure of the dura of the middle fossa at operation; (2) as assistance in selecting the most extensively involved ear in bilateral mastoiditis; (3) as an additional indication for mastoidectomy; (4) in the diagnosis and drainage of an extra dural abscess, and possibly in the prevention of this complication. Patients with unilateral scalp tenderness often complain of shooting pains to the corresponding eye and sharp, intermittent shooting pains deep within the ear of the same side. At operation, the author has been impressed by the marked zygomatic destruction and extensive involvement of the dura of the middle fossa, which he has encountered more frequently in adults over fifty years of age. After a recitation of 6 illustrative cases and of 2 paradoxical ones, Dixon enters upon a

neurologic consideration of the reasons for scalp tenderness in cases presenting middle-fossa dural involvement and states that "it is quite evident that the fifth nerve is intimately connected with the dura of the middle fossa. Also it is a well-known fact that nerves passing through the Gasserian ganglion are quite susceptible to disturbances of sensation."

A Study of Acute Infection of the Respiratory Tract in the Ape.—During an investigation of the type of acute infections of the human upper respiratory tract usually grouped under the term "Common Cold," DOCHEZ, SHIBLEY and MILLS (*Proc. Soc. Exper. Biol. and Med.*, 1929, **26**, 562) selected as the animals for investigative purposes the anthropoid apes, inasmuch as they not only frequently suffered from "Common Colds," but that the source of infection was a human being, similarly afflicted. It was found that, during periods of normal health, the upper respiratory flora resembled, in respect to bacteria present, that of the human upper respiratory tract to a surprising degree.[1] During the period of observation a number of the animals contracted upper respiratory infections presumably from chance human contacts and the marked increase in numbers and spread in area involved by the potentially pathogenic bacteria already present in the upper respiratory passages was one of the striking features of the picture. In an attempt to communicate by means of a filterable agent a respiratory infection comparable to the human cold, filtrates of nasopharyngeal washings from early human cases with a "Common Cold" were introduced intranasally into several apes. Of the first 7 animals so inoculated, 3 contracted upper respiratory infections similar in their manifestations to the spontaneous infections of the simian and to the "Common Cold" in human beings. The incubation period of the experimental infection was about thirty-six hours. The nature of the active filterable agent is as yet unknown. From the filtrate in all positive experiments an anaërobic bacillus of the type described by Olitsky and Gates was cultivated.

Investigations of Diphtheria Carriers.—In presenting a statistical study on human carriers of *B. diphtheriæ*, KOLLMANN (*Arch. f. Kinderh.*, 1929, **86**, 185) found that of 3062 children, 418 (13.6 per cent) harbored the Klebs-Loeffler bacillus in their upper respiratory passages. The carrier state was encountered most frequently in younger children; and in 38 per cent of newborn infants. The number of carriers increased during the winter, spring and autumn; also, among those children living in unhygienic environment, and in those who had gastrointestinal disturbances and pathologic states in their nasopharynges. The incidence of morbidity paralleled that of the carrier state. Most favorable therapeutic response followed isolation and topical application of silver nitrate solution (2 per cent).

[1] Shibley, Hanger and Sachez with the assistance of Mills (Proc. Soc. Exper. Biol. and Med., 1926, **22**, 258.) See Retrospect: AM. JOUR. MED. SCI., 1926, **172**, 300.

RADIOLOGY

UNDER THE CHARGE OF

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Effect of Ultraviolet Light on the Blood.—Of thirty-one abnormal cases studied by DORNE (*Arch. Phys. Therap, X-ray, Radium*, 1929, **10**, 296) there was a definite decrease of the red blood cells in those cases receiving a general exposure. The white blood cells and lymphocytes were definitely increased in those cases irradiated by the fractional method, and general irradiation produced no appreciable difference. The hemoglobin was slightly increased by both methods. Coagulation time was decreased in 60 per cent of the cases. Blood platelets were increased 100 per cent in every case studied.

The Visualized Esophagus in the Diagnosis of Diseases of the Heart and Aorta.—RIGLER (*Am. J. Roent. and Rad, Therap.*, 1929, 21, **563**) strongly recommends visualization of the esophagus with barium for roentgenologic examination of the heart and aorta. A very thick barium paste is used, which the patient holds in his mouth, swallowing it only when all preparations have been made. Roentgenoscopic examination is made in the posteroanterior, right and left oblique and right lateral positions. Dilatation of the left auricle is an early and fairly constant sign of mitral disease, and its absence makes a diagnosis of mitral disease very doubtful. Such dilatation or its absence may be proved by examination of the esophagus which is displaced posteriorly and compressed when the left auricle is enlarged. It may also be displaced to the right, rarely to the left. Using the esophagus as the right border, a more accurate transverse measurement of the transverse and descending portions of the aortic arch can be made. Dilatations of the arch will produce deviation to the right and posteriorly and compression of the esophagus. The actual size of an aneurysm can be clearly delineated. Tortuosity and lengthening of the descending aorta, such as occur with arteriosclerosis and hypertension, can be graphically demonstrated by distortion of the esophagus, which accompanies the aorta in its course. Dilatations, either local or general, of the descending aorta produce anterior displacement and compression of the esophagus. If the dilatation or aneurysm is in the proximal three-fourths, there may also be displacement to the right; if in the distal one-fourth, there may be displacement to the left.

Radiation Treatment of Cancer of the Breast.—In the experience of PFAHLER and WIDMANN (*Am. J. Roent. and Rad. Therap.*, 1929, **21**, 546) recurrent cancers of the breast with glandular and mediastinal metastasis show a postoperative life of forty-five months with irradiation, as

compared with twenty-seven months when surgery alone is used. Inoperable primary cases show an average life of fifty-four months when treated by radiation, as compared with thirty-four months when no treatment is given. In an average of the statistics from ten clinics in which surgery and irradiation were used, 58.3 per cent three-year and 43.2 per cent five-year cures, as compared with the surgical results alone in thirty-two clinics in which there were only 38.6 per cent three-year cures and 28.8 per cent five-year cures. The writers therefore recommend irradiation in all cases of cancer of the breast, with or without surgery, according to the indications.

The Effect of Roentgen Rays on the Gall Bladder: Experimental Production of Cholecystitis.—A definite acute and chronic cholecystitis was experimentally produced by BRAMS and DARNBACHER (*Radiology*, 1929, **13**, 103) in a series of dogs with dosage of Roentgen rays that are within the range of those used for therapeutic purposes. The changes produced are destructive. They consist of hemorrhage, inflammatory edema, round-cell infiltration, fibrous tissue hyperplasia, and, in some instances, necrosis of the epithelium, and resemble the type of cholecystitis produced by chemical means. Basing their opinion on the relative lack of injury to the exposed portion of the duodenal and pyloric mucosa, the authors believe that the gall bladder epithelium is comparatively more sensitive to Roentgen ray exposure than the other organs in apposition to it. Hence the possibility of injury to the gall bladder by deep therapy in the region of the right upper quadrant must be borne in mind.

Pulmonary Syphilis.—A case of syphilis of the lung in a woman thirty-nine years of age is reported with illustrations by ALLISON (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 21). Roentgenograms made during an attack of influenza showed a nodular consolidation extending out from the root of the right lung and invading the parenchyma of all three lobes. The shadow of the right diaphragm was faintly visible trough a thickened pleura which partially obscured the lower half of the chest. Six months later roentgenograms showed a definite extension both of the pleural thickening and the pulmonary consolidation. The lesion resembled an infiltrative type of Hodgkin's disease. One month afterward, and approximately three weeks after treatment with salvarsan and mercury was instituted, a third set of films showed remarkable resolution of the process. After four months of treatment the lesion had almost completely disappeared.

The Effect of Iodized Oils on Serous Membranes.—From experiments on dogs, GRANDALL and WALSH (*Radiology*, 1929, **12**, 499) conclude that lipiodol and lipoiodin are irritating to certain serous membranes. Intrapericardial injection produces pericarditis with effusion, followed by death in about two weeks. Intrapleural injection produces a pleuritis of variable grade; some animals die. Injection into joints produces some inflammation of the capsule. Intraperitoneal injection appears to be harmless. Poppy-seed oil and ethyl brassidate are equally as irritating to the pericardium as their iodin compounds; sesame oil is somewhat less irritating, while olive oil appears to be practically innocuous.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Arteriosclerotic Parkinsonism. — MacDonald Critchley (*Brain*, 1929, **52**, 23) makes an extensive review of the literature for the purpose of calling attention to Parkinsonian symptoms in connection with the arteriosclerotic syndromes. From this study he arbitrarily divides the entire group into subtypes, Type I being characterized by rigidity, fixed facies and short-stepping gait. Type II is similar to Type I with the addition of pseudobulbar manifestations. Type III is similar to Type I but with the addition of dementia and incontinence of urine and feces. Type IV is similar to Type I with signs of pyramidal disease but without pseudobulbar manifestations. Type V, as Type I, but with superimposition of cerebellar symptoms. He reviews the symptomatology and pathology in great detail and compares the arteriosclerotic syndromes with postencephalitic, senile and idiopathic forms of Parkinsonism. He believes that in association with cerebellar arteriosclerosis, incomplete pictures of Parkinson's disease are more common than complete pictures and all degrees of involvement may occur. The chief differential points between arteriosclerosis and idiopathic varieties are that the arteriosclerotic cases may commence suddenly, although an insidious onset is more usual; the progression is more rapid and may proceed by a series of abrupt exacerbations; the age of onset while approximately the same in the two conditions is of some value, as very early or very late onset is suggestive of a vascular basis; the tremor is usually absent in the sclerotic cases, the muscles feel firmer to the touch and the rigidity is often characterized by a superadded tendency toward catatonia; many of the arteriosclerotic cases show bulbar signs and emotional incontinence or may show a more or less profound dementia; and evidence of focal cerebellar symptoms, of peripheral arteriosclerosis, or of high blood pressure suggests the arteriosclerotic type. The blood pressure, however, may be low in the senile or decrescent types. The essential pathological features are lesions in the globus pallidus and in the substantia nigra but changes at other levels can be demonstrated as contributing toward the rigidity. He believes that Parkinsonism is a syndrome which may occur under numerous pathological circumstances, depending upon the site rather than the nature of the disease.

A Form of Myasthenia Gravis with Changes in the Central Nervous System.—Douglas McAlpine (*Brain*, 1929, **52**, 6) presents a case of myasthenia gravis occurring in a female, aged twenty-three years. Onset

with dysarthria at twenty-two years, followed by diplopia and fatigability, especially in the evening. A year later she showed physically, bilateral and variable ptosis, diplopia, weakness of the orbicularis oculi and of the lower facial musculature. Fatigue was easily inducible in the soft palate, tongue and limbs. Reflexes and sensation were normal. Exitus after fifteen months of illness in a dyspneic attack. Autopsy showed no gross abnormalities of brain or spinal cord. Histologically the visceral and endocrine organs were normal except that the thymus gland was markedly hypertrophied. Cerebral cortex, subcortical white matter and basal ganglia were normal except for a mucocytic degeneration, especially involving the white matter. Motor nuclei in the brain stem were unaltered except that a few cells at each third nucleus showed slight changes. The vessels were normal. The spinal cord showed marked infiltration of the bloodvessels with round cells and a slight degree of gliosis, especially around the anterior horns, but the motor cells were normal at all levels. Mucocytes were more prevalent in the spinal cord than elsewhere. He considers the possibility of myasthenia gravis being related to epidemic encephalitis but after review of the literature he concludes that no definite relationship is to be demonstrated in any of the cases so far reported. The marked inflammatory reactions evident in his own case he considers to support the idea of such a connection to some extent, especially as mucoid degeneration is more often associated with epidemic encephalitis than with other organic brain diseases. The same considerations lead him to conclude that his own case does not fall into any previously described clinicopathologic group. "It is concluded from a study of the case that there is a form of myasthenia gravis associated with inflammatory changes in the central nervous system, the cause of which is at present problematical."

A Case of Relapsing Interstitial Hypertrophic Polyneuritis.—HARRIS and NEWCOMB (*Brain*, 1929, **52**, 108) present a case differing clinically from that of Dejerine and Sottas yet showing the same pathologic picture. The chief difference lies in the recurrent attacks resembling polyneuritis over a period of six years with complete recovery between the attacks. The last attack lasted twelve months with muscular wasting and foot drop and terminal attacks of choking, dyspnea and finally paralysis of the diaphragm due to involvement of the vagus and phrenic nerves. They find no previous case, identical to this, with necropsy, in the literature. They believe that the Dejerine and Sottas type of familial hypertrophic interstitial neuritis should be distinguished as a separate group from recurrent polyneuritis, although the hypertrophic changes found in this case forms a remarkable link between the two groups and both may be due to a similar cause.

Death Following Cisterna Puncture.—PINEAS (*Der Nervenarzt*, 1929, **1**, 25) states that very few cases with death following cisterna puncture have been reported. He reports the case of a man, aged fifty-six years, who had been considered as cerebral lues with a negative blood and spinal fluid Wassermann. The Pandy and Nonne tests were both 4+; gold sol 221100; mastic 122200. He had previous lumbar puncture and on August 6, 1927, cisterna puncture was performed with the patient

in the sitting position. The needle was inserted 6 cm. without obtaining any fluid. It was withdrawn and a second needle was inserted about 5 cm., but no fluid was obtained. As an attempt was made to push the needle a little deeper the patient collapsed, so the puncture was abandoned and the patient placed in bed. He had a bigeminus pulse and Cheyne-Stokes respiration. He improved somewhat after the administration of stimulants but died about nine hours after the puncture. At autopsy, they found a generalized chronic vascular change of extreme degree. The vessel walls were greatly thickened, both in the brain and spinal cord. The paths of the two needles were seen in the pia and there was a marked subpial hemorrhage. In varied locations (brachia pontis, the sensory vagus nucleus, and so forth). they found bloody extravasation immediately surrounding the vessels. The vessels of the fourth ventricle were enlarged with very thick walls and bound together in a fibrous mass with the medulla and the cerebellum. At the site of the needle punctures in the pia were two vessels which had been penetrated and extruded blood on pressure. He considers that the chronic changes in the bloodvessels were predisposing factors to the lethal result of cisterna puncture. In spite of the exitus the author considers that the large number of cases that have been successfully performed makes this procedure still desirable but he believes it should be performed with extremely careful technique and even then in some cases may not be entirely free from accidents.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Researches on the Titer of the Blood Lipase in Different Forms of Tuberculosis.—MICOLAU and ANTINESCU (*Arch. roum. de pathol. exper.*, 1928, **1**, 437) studying the blood lipase in 30 cases of tuberculosis, with especial involvement in different instances of pulmonary parenchyma, bone, serous membranes, and meninges, found the titer of the ferment well maintained in the incipient stages of the disease but considerably diminished in the graver forms of the malady The more acute types of tuberculosis with miningeal involvement showed little diminution of the blood lipase. It appeared that the lipase titer varied more in proportion with the general state of the disease than with the degree of advancement of a local tuberculous lesion. Its reduction was associated with an unhappy clinical course and unfavorable prognosis. In 9 cases, in which the lipase in pleural or peritoneal fluids was determined, its titer was approximately half the titer of the serum lipase. The lipase ferment was not found in the cerebrospinal fluid of conditions of tuberculous meningitis, but neither

is its presence demonstrable normally. The lipase occurring in the blood was found to be a serum lipase, as evidenced by its reactions to quinine, atoxyl and sodium fluoride; pancreatic and hepatic lipases were not demonstrable in the blood serum. The resistance of serum lipase to quinine varies with the titer of the ferment, being greater when the lipase is more active while atoxyl and sodium fluoride also inhibit its action.

Laboratory Infection with Bacillus Typhosus.—Little is known about many of the conditions of infection with the Gram negative pathogenic bacilli of the intestinal tract. The accidental infections in laboratories which have occurred from time to time have been brought together and analyzed by KISSKALT (*Arch. f. Hyg. u. Bakteriol.*, 1929, **101**, 137). The cases from a previous report in 1915 are included and a number of most interesting facts are given. There were 39 cases of infection with pure cultures of Bacillus typhosus in which the moment of infection was known. Of these 6 were fatal, 6 very severe, 5 severe, 10 rather severe 8 were mild and in 4 severity was not mentioned. The incubation period of 32 cases varied between three and twenty-one days, and in 14 of the 32 it was under fourteen days. Some of the responsible cultures had been on media for a long time, while others were but recently isolated. The number of bacilli entering the oral cavity was usually large but not necessarily so, and a number of cases are reported in which although the bacilli were taken into the mouth the infection did not follow. This latter type of case is usually kept secret so that the percentage of those receiving the bacilli who became ill cannot be determined. A group of cases in which the infection with pure cultures was most probable, another group in which it clearly appeared to have occurred in the laboratory but in which it was not known whether from cultures, stools or urine, and a third group in which the infection was from either intestinal contents or blood, all add to the interest and value of the report. A number of examples of laboratory infections with other bacteria help to strengthen the impression that laboratory infections are not as uncommon as is generally believed.

HYGIENE AND PUBLIC HEALTH

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A Study of Diphtheria Mortality.—LUCIA (*Univ. of Calif. Pub. Health* 1929, **1**, 247) made statistical comparisons of diphtheria mortality in three age groups in relation to conditions of urban and rural populations

and established the following relations: (*a*) Deaths in the 0 to 4 age group during a year of low incidence are most likely to occur in urban populations, especially in industrial communities, among the illiterates who live under crowded conditions, and where there is concentration of child population. An increase in the number of homes tends to reduce the number of deaths from this disease, as does also an increase in the number of persons engaged in farming occupations. Negroes also correlate negatively with deaths in this age group. During an epidemic, urban population with its accompanying industrialism does not tend to proportionately increase the number of deaths in the 0 to 4 age group. On the other hand, more complete dissemination of the organism produces a higher mortality in rural sections of the country where there are many susceptible children. (*b*) Deaths in the 5 to 9 age group are more prevalent in cities over 25,000 population in a year of low diphtheria incidence. A high mortality is associated positively with manufacturing industries, child population concentration, and, to some extent, with illiteracy. Where there are many negroes, many homes per unit population, and much farming, the number of deaths is low. During an epidemic year the mortality in this age group increases in cities, and rises in proportion to the number of homes, number of persons engaged in farming occupations, and number of children in the 0 to 4 age group. The number of deaths, however, drops in inverse proportion to the urban population, number of illiterates, and negro population. (*c*) Deaths in the 10 and over age group in a nonepidemic year occur in direct relation to the number of homes, and in a lesser degree, to the number of persons engaged in manufacturing occupations. There are comparatively few deaths in this age group among illiterates and negroes. During a year of high incidence, the 10 and over age group mortality rises among persons engaged in farming occupations, but drops among those engaged in manufacturing occupations. It remains high in relation to the number of homes. (*d*) Deaths among all age groups, in a year of low diphtheria incidence, usually occur in relation to urban communities where there are great chances of infection by contact because of overcrowding. Under epidemic conditions, the high mortality shifts from urban to rural communities, when increased dissemination makes possible the spread of infection to the great reservoir of susceptibles in country districts. (*e*) Better social and economic conditions tend to protect children of the 0 to 4 age group from diphtheria, and thus to build up a large group of susceptibles in the later age groups who suffer high fatalities especially during epidemics. (*f*) There is a rise in ratio of the number of deaths in the 5 to 9 age group to the number in the 0 to 4 age group across the United States from south to east, and east to west. This rise seems dependent upon the differential effect of certain population variables, for example, number of homes per unit population, illiteracy, etc. (*g*) The secular trends of the ratios of the number of deaths in the 5 to 9 age group to the number in the 0 to 4 age group are upward in all sections of the country. This tendency may be the effect of the epidemic year of 1921 or it may indicate that, since the 5 to 9 age group is beginning to participate in diphtheria mortality to a greater extent, an increased general diphtheria mortality may be expected. (*h*) Judging from experience in the large cities of the Atlantic coast, writers on diphtheria tend to stress

artificial immunization of the 0 to 4 age group, rather than of the 5 to 9 age group. It is apparent from this study of mortality that the immunization of school children should not be neglected, at least in the western states. (*i*) Although the actual number of diphtheria deaths occurring in children of ages 0 to 4 years is greater than in those of ages 5 to 9, a proportionate mortality for the 5 to 9 age group of 16 per cent, as compared with a proportionate mortality for the 0 to 4 age group of 3 per cent, indicates that diphtheria is an important cause of death in the 5 to 9 age group. This is an additional reason for directing efforts toward immunization of this group.

Rocky Mountain Spotted Fever. A Preliminary Report on the Weil-Felix Reaction.—KERLEE and SPENCER (*U. S. Pub. Health Rep.*, 1929, **44**, 179) found that the serum of rabbits and of humans suffering from, or convalescent of, Rocky Mountain spotted fever gave a positive reaction with certain strains of the proteus organism. This is a point of similarity between this disease and typhus fever.

A Study of the Relationship between Type of Ventilation and Respiratory Illness in Certain Schools of New Haven, Conn.—GREENBURG (*U. S. Pub. Health Rep.*, 1929, **44**, 285) reports studies on 2052 people in mechanically ventilated schools and on 1546 pupils under window ventilation. The results of the observations seem to clearly favor window ventilators, the figures for the latter group showing absences for respiratory conditions about half as large as those for the mechanically ventilated units. The exact cause of this difference was not determined. The conclusion has the following final paragraph taken from the report of the New York State Commission on Ventilation: Because window ventilation is practicable for the ordinary schoolroom it does not follow of course that the assembly room, the theater, and other places seating, in certain cases, many people can also be dealt with in this manner. Each type of inclosure must be handled as a distinct problem. Natural ventilation has its limitations. That the schoolroom is not beyond these limitations is indicated by this study.

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